Summary of Public Comments Received on the 2022 Draft IRIS Toxicological Review of Formaldehyde (Inhalation)

This table provides a comprehensive summary of public comments on the 2022 draft assessment received through the EPA docket 'Toxicological Review of Formaldehyde Inhalation Toxicity' (see https://www.regulations.gov/docket/EPA-HQ-ORD-2010-0396), where the full set of comments as submitted are available. This compilation does not include public comments submitted directly to the National Academies of Sciences, Engineering, and Medicine (NASEM) after announcing the external peer review in 2022. It also does not include comments submitted to the EPA docket regarding the 60-day length of the public comment period or a requested correction to an affiliation. Comments are divided into two tables (Tables 2 and 3), with a legend of public commenters and abbreviations provided in Table 1. Table 2 compiles "Assessment-Specific Comments," organized, to the extent possible, by external peer review charge questions, and further broken down by topic area and commenter. Table 3 compiles "Other Comments," which includes comments considered outside the scope of the IRIS formaldehyde assessment and the peer review charge questions. Comments that have been truncated or which have additional details or supporting information in the docket are noted as such.

[Disclaimer: while EPA made every effort to accurately and comprehensively compile the submitted public comments in these courtesy tables, it is possible some information could be missing or inaccurate. Footnote callouts were deleted, and a few minor grammatical corrections were made to some comments for clarity. The EPA docket is the primary source that should be consulted for comments on this assessment.]

Table 1. Public Commenter Legend

ACC: American Chemistry Council	**Ram: Ramboll**
AFPA: American Forest & Paper Association	**RM: Roger O. McClellan**
Anon: Anonymous	**SV: ScitoVation**
AVMA: American Veterinary Medical Association	**TS: Thomas B. Starr**
Cardno: Cardno ChemRisk (now Stantec)	**TERA: Toxicology Excellence for Risk Assessment**
EDF: Environmental Defense Fund	**ToxStrat: ToxStrategies**
Form: Formacare	**Troy: Troy Corporation**
ILMA: Independent Lubricant Manufacturers Association	**UCSD: University of California San Diego**
LCA: Louisiana Chemical Association	**UCSF: University of California San Francisco**
MCSC: Monell Chemical Senses Center	**UNC: University of North Carolina at Chapel Hill**
NRDC: Natural Resources Defense Council	**USCC: United States Chamber of Commerce**
PEA: U.S. Poultry and Egg Association	

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Comment Period: April 14, 2022 – June 13, 2022

Table 2. Assessment-Specific Comments

Comment	Commenter (PDF #; page)	Charge Question(s)	EPA Notes and *Topic Characterization*
General Comments and Charge Question 1: Assessment Methods and Organization			
"Overall, we appreciate the evaluation. It is a thorough and well-reasoned scientific evaluation of the inhalation risks of formaldehyde, including both cancer and non-cancer health endpoints."	NRDC (1)	1	*General comment*
"EDF applauds EPA's Office of Research and Development's IRIS program for a thorough, clear, well documented robust assessment that clearly demonstrates that the IRIS program heeded the advice of the National Academies of Sciences, Engineering, and Medicine (NASEM) in their 2014 and 2018 reports on the IRIS program."	EDF (1)	1	*General comment*
"... we strongly encourage EPA to revise the 2022 draft IRIS assessment and incorporate the best available science and practices for systematic review. A formaldehyde IRIS assessment that does not consider the weight of scientific evidence could lead to unwarranted regulations that would ripple through the supply chain."	USCC (6)	1	*General comment*
"Ensuring and maximizing the quality of the 2022 Draft Assessment requires the application of 'a "weight-of-evidence" approach that considers all relevant information and its quality [...].' Equally important, the substance of the information must be 'accurate, reliable and unbiased,' which entails the use of 'the best available science and supporting studies conducted in accordance with sound and objective scientific practices [...].' EPA must ensure that the information presented in the 2022 Draft Assessment 'is comprehensive, informative, and understandable.' "Due to a deficient systematic review, information that was, or should have been, known to the Administrator was excluded from the Draft Assessment." "The 2022 Draft Assessment does not fully incorporate NASEM (2011) systematic review recommendations or current best practices for implementing systematic review in chemical toxicity assessments." "The 2022 Draft Assessment does not follow guidance in the IRIS Handbook. The 2022 Draft Assessment makes no specific reference to the IRIS Handbook with the exception of a single footnote. However, some of the general processes mirror, at least in part, the IRIS Handbook. In other parts, it deviates from the IRIS Handbook more substantively. There are several places in the 2022 Draft Assessment with language and tables that are borrowed from the IRIS Handbook, but, in some cases, subtle changes were made that, while easily missed, are not unsubstantial." "The 2022 Draft Assessment does not consider IRIS Handbook recommendations regarding MOA."	ACC (0100; 8, 17, 59) ACC (0103; 5, 8, 19, 20)	1, 1a, 1b	*General methods comment; Responsiveness to NAS (2011); IRIS Handbook* EPA Note: the systematic review (SR) methods developed and applied in the draft assessment to make it responsive to the NAS (2011) report served as the basis for many of the methods in the IRIS Handbook (and thus the methods are consistent). The IRIS Program sought feedback from the NAS on the evolving IRIS SR methods in 2014 and

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"The frequent and inconsistent use of subjective terms, results in an overly complicated Draft Assessment that is confusing and difficult to interpret. As shown in Table 1, the term "low concentration" can range from about 0.002 to 0.4 mg/m^3, "high concentration" from about 3 to >12 mg/m^3, and "excessive concentrations from about 7 to ≥20 mg/m^3, the overlapping and ill-defined subjective terms makes interpretation of statements such as those highlighted in Table 2 almost impossible to put into context. The level of subjectivity in the language used in the Draft Assessment must be reduced to increase transparency in study interpretations." "There are many instances of language supporting a subjectively predetermined outcome." "The Draft Assessment frequently combines "statistics not reported" with "not statistically significant" and undefined "significant" determinations. The basis for statistical and biological relevance as treatment-related is not transparent." *[Please see docket for details and supporting information]*			2018 and, in 2020-2022, the completed draft IRIS Handbook received public comment and peer review by NASEM[1]. Note that NAS (2011) indicated EPA should not wait until SR is fully implemented to produce IRIS assessments.
"Overall, the document is difficult to follow as pertinent information is scattered amongst three separate documents: an Assessment Overview, a Toxicological Review, and Supplemental Information. This reviewer found it difficult to follow the assessment whether reading printed hard copies or a computer screen. In some places there are lengthy passages without any supporting references, making it difficult for the reader to know which studies the U.S. EPA is using to support a given statement, even for readers familiar with the formaldehyde literature. As written, topics are covered in differing degrees of depth in multiple places. Perhaps an alternative approach would be to have combined the Assessment Overview and Toxicological Review into two or three separate documents with as minimal overlap as possible. Possible alternatives include portal of entry (POE) vs systemic effects or cancer vs non-cancer effects—perhaps with dose-response analysis in a separate document altogether. The current approach needs serious reconsideration."	ToxStrat (19-20)	1	*General methods and organizational comment* EPA Note: the Assessment Overview is a summary of the Toxicological Review and Appendices; the Overview is provided as a courtesy that may be useful to some readers.
"The extent to which EPA has addressed the 2011 NAS recommendations is unclear. We are generally concerned with whether the 2011 NAS recommendations for the formaldehyde assessment were fully taken into consideration in this assessment. Given the critical feedback from the NAS, we were surprised to see that the NAS report is rarely mentioned in the draft Formaldehyde Toxicological Review. It would be appropriate to more thoroughly outline how changes to the assessment were incorporated to address the concerns raised by this committee of experts."	UCSF (4)	1a	*General methods comment; Responsiveness to NAS (2011)* EPA Note: The responses to NAS

[1] https://nap.nationalacademies.org/catalog/26289/review-of-us-epas-ord-staff-handbook-for-developing-iris-assessments (2022)
https://nap.nationalacademies.org/catalog/25086/progress-toward-transforming-the-integrated-risk-information-system-iris-program (2018)
https://nap.nationalacademies.org/catalog/18764/review-of-epas-integrated-risk-information-system-iris-process (2014)

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			(2011) comments are in Appendix D.
"Based on the 2010 National Academy of Sciences (NAS) IRIS formaldehyde review and their 2011 recommendations to the EPA it [is] difficult to discern if these were followed in the preparation of the current assessment. The 2010 NAS document clearly indicated EPA did not identify modes of action and failed to utilize a "weight of evidence" approach towards endpoints such as nasal pharyngeal cancer (NPC), sino-nasal cancer, lymphohaematopoietic cancer (LHP), nervous system effects and systemic toxicity. Unfortunately, the 2022 IRIS assessment also did not follow these recommendations and many of the conclusions for these endpoints are the same as in 2010." "It was difficult to assess and understand EPA's conclusions for many of the toxicological endpoints identified in the assessment and this was compounded by the incorporation of the draft IRIS Handbook recommendations and additional explanation on the process for the determination of the acceptability of studies. EPA's approach towards endpoint selection is inconsistent and confusing since it is not clear if they followed a) the recommendations in the draft IRIS handbook or chose another approach."	Troy (1)	1	*General methods comment; Responsiveness to NAS (2011); IRIS Handbook*
"We wanted to address the Agency to the fact that two of our Formaldehyde (FA) manuscripts were not cited in the Review (Golden 2011, Golden and Holm 2017). It is important to note that these manuscripts report on critical aspects in the FA literature that have not been addressed in the Review. Including this information would supply useful perspective on the complex literature regarding the relationship between FA and asthma and sensory irritation and lead the Agency to different conclusions. EPA also does not include or discuss other publications that deserve more careful consideration. Our examination of the Review shows the following: • EPA relies on two papers to derive a Point of Departure (POD) for asthma that show no positive association with the disease • EPA failed to review and incorporate critical and relevant literature • EPA failed to discuss studies accurately and transparently • These failures have led to the lack of a proper Weight of Evidence integration using the Best Available Science • EPA is overly conservative in its use of uncertainty factors leading to 'acceptable concentrations' that are far below other recent regulatory evaluations of FA that use a practical Weight of Evidence approach • This conservatism has led to EPA-derived 'acceptable' concentrations that exist in virtually no locations on earth."	AFPA (0073; 1-2)	1, 5	*General methods comment; Literature search and screening; RfC* EPA Note: Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.

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"EPA did not clearly develop a pre-published protocol. EPA, in its Charge Questions to the Peer Review Committee, stated that 'The IRIS Program decided to conduct a reassessment of formaldehyde inhalation from scratch on the basis of that review, using transparent and predefined systematic review methods.' We are deeply concerned that we were unable to find an IRIS Assessment Plan or Protocol released in advance of the assessment for peer review comment. Although there were myriad delays of this document, it is troubling that such a protocol may not have been released, which violates the IRIS process for conducting assessments and the stated intent to used 'transparent and predefined systematic review methods.' We have commented extensively on the importance of pre-defined protocols, which are foundational to such assessments and play an important role in reducing bias and ensuring transparency.[15,16]"	UCSF (4)	1a	*Scoping/Protocol* EPA Note: As noted above, NAS (2011) made it clear that EPA should not wait until SR is fully implemented to produce IRIS assessments. SR enhancements such as releasing protocols, are a relatively recent activity (begun in 2018). The current formaldehyde draft was in progress well before this timeframe. While EPA did not publicly release a specific protocol in advance, the methods described in the Preface and used to develop the draft are consistent with the current SR methods outlined in the IRIS Handbook, which has been peer-reviewed by NASEM (see footnote 1). Further, the key science issues and chemical-specific considerations that IRIS assessment protocols

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			describe were detailed in NAS's (2011) report, which directly informed the current draft.
"In developing the 2022 Draft Assessment, EPA failed to fully implement this first step. EPA never released an IRIS assessment plan, which would have included scoping and problem formulation materials. Rather, on its website it states that this step is "not applicable" without explaining why this step is not applicable. By not following the IRIS process, EPA denied the public multiple opportunities to provide valuable input into key formative elements of the 2022 Draft Assessment. Consequently, the 2022 Draft Assessment was not based on a fully developed record of available information." "The 2022 Draft Assessment does not discuss scoping or problem formulation activities for the "newly developed" assessment...Consistent with the recommendations from the NASEM (2011) review of the 2010 Draft Assessment, EPA should have engaged in an explicit scoping and problem formulation process to specifically address best available evidence-based health outcomes in the context of mode of action." "...The 2022 draft Formaldehyde Review contains no discussion of problem formulation activities or an Assessment Plan. There is very little discussion of how EPA arrived at the Populations, Exposures, Comparators, and Outcomes (PECO) statements, and no discussion of EPA' s hypotheses regarding critical endpoints for formaldehyde assessment. To meet the NASEM recommendations, EPA should have organized the draft Formaldehyde Review around plausible MOAs and/or hypotheses regarding the most critical formaldehyde effects. At a minimum, EPA should revise the draft to include discussion regarding problem formulation and scoping activities that occurred in 2012 and again in 2021, particularly considering the many changes to the IRIS Program in the 10 years between initiation of the assessment and its release." "For example, EPA has not planned, issued, nor taken comment on a systematic review protocol for formaldehyde, unlike the other sixteen chemicals to be assessed according to the Agency's February 2022 IRIS Program Outlook. However, the Feb. 8 EPA letter claims that "[t]he systematic review methods used in the current draft IRIS formaldehyde assessment formed the basis for the methods presented in the IRIS Handbook, which was favorably reviewed by the NASEM in November 2021." While subsequent process-oriented reviews[7] may offer context to the panel reviewing the 2022 IRIS assessment, they do not resolve NASEM critiques of the previous IRIS assessment of formaldehyde." *[Please see docket for details and supporting information]*	ACC (0103; 8, 75) ACC (0083a; 3) ACC (0092; Attachment #4, 2)	1, 1a	*Scoping/Protocol* EPA Note: [also see note above]; some recommendations attributed to NAS (2011) could not be confirmed (e.g., on a process for scoping and problem formulation). However, the NAS (2011) report did include advice on improving the approach to IRIS assessment development more generally, while noting in their Summary: "The committee recognizes that revision of the approach will involve an extensive effort by EPA staff and others, and it is not recommending that EPA delay the revision of the formaldehyde assessment to implement a new approach."

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"U.S. EPA's literature search and/or review of their literature search results incorrectly filtered out relevant MOA evaluations that the agency should have considered."	ToxStrat (2)	1	*Literature search and screening*
"Attached are several recent articles and reviews which may be relevant to EPA and NASEM reviewers, including several peer-reviewed pieces published since 2000 which do not appear in the main text or appendices of the draft assessment. [Hartwig et al. 2020; Chang et al. 2021; Protano et al. 2021; Agathokleous and Calabrese 2021]" *[Please see docket for details and supporting information]*	Anon (0090; 1)	1	*Literature search and screening* EPA Note: Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.
"It is unclear what EPA used for its study inclusion and exclusion criteria. For example, NIEHS comments expressed concern that EPA's literature search was inadequately broad, and unjustifiably limited. NIEHS noted that, "the limited set of search terms is unlikely to capture all animal studies of hypersensitivity" and may exclude other important studies. Moreover, the public is unable to fully access the Systemic Evidence Maps, which are crucial to convey critical information such as how the study inclusion and exclusion criteria were applied to particular studies, and how that may limit the data set used for the evaluation. NIEHS identified this concern as "Tier 1 – Necessary Revision", which NRDC agrees with."	NRDC (2)	1	*Literature search and screening* EPA Note: the systematic evidence map used to update the literature from 2016-2021 is in Appendix F, not a separately released file. Interagency reviewer (e.g., NIEHS) comments were on a draft prior to revision for public release. Please consult the full interagency review comments in the EPA docket.
"...While there is an extensive section of text denoting criterion for assessment study selection it is not clear why certain studies were chosen for a particular toxicological endpoint." "In addition, the assessment literature review did not capture many of the new more recent scientific studies industry has prepared since the last IRIS assessment. Since 2010, there has been a continual effort by industry and academia alike to provide additional data on key formaldehyde inhalation toxicological endpoints. This new data adds to an already extensive data set on this compound. These new studies include the reanalysis of epidemiology studies,	Troy (1-2)	1	*Literature search and screening* EPA Note: Reviews and studies with no primary data are considered as

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examination of the effects of endogenous versus exogenous formaldehyde and portal of entry effects, examination of formaldehyde exposure to asthma, mode of action studies and sub-chronic animal inhalation studies. In total approximately 73 additional studies have been conducted and, based on the current assessment, have not been incorporated into the current document."			supplemental materials and tracked in HERO.
"These comments are directed at EPA's discussions of the collaborative research conducted by myself and Dr. James A. Swenberg on a novel "bottom-up" approach to bounding human cancer risks that could arise from chronic inhalation exposure to low levels of airborne formaldehyde. This work has been described in three peer-reviewed publications (Swenberg et al. 2011, and Starr and Swenberg 2013 and 2016). It has also been addressed critically in a "Letter to the Editor" by Crump et al. (2014), and our response to that letter (Starr and Swenberg 2014), the latter of which is not discussed or even cited in the Draft IRIS Toxicological Review, its reference list, or the Supplemental Information for Formaldehyde document. More recently, Hartwig et al. (2020) and Lu et al. (2022) have reviewed (positively) the "bottom-up" approach in two additional peer-reviewed articles, neither of which is discussed or cited in these EPA documents. EPA's failure to cite our response to Crump et al.'s 2014 letter and the two more recent peer-reviewed articles calls into question the completeness (and validity) of EPA's Systematic Review process."	TS (1)	1	*Literature search and screening* EPA Note: Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.
"Moreover, over the last decade, more than 40 peer reviewed studies have demonstrated safe thresholds for formaldehyde, including important methodologies published in recent weeks, award-winning re-analysis of key data, and several lines of evidence demonstrating the safe use of formaldehyde for EPA regulatory purposes. For example, 'A Review of Stable Isotope Labeling and Mass Spectrometry Methods to Distinguish Exogenous from Endogenous DNA Adducts and Improve Dose–Response Assessments' published by the American Chemical Society in December 2021. Unfortunately, many of these high-quality studies and reviews are ignored, briefly dismissed, or misused by EPA in the draft assessment (as noted in comments filed by the Small Business Administration)."	USCC (3)	1	*Literature search and screening* EPA Note: Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO. Interagency reviewer (e.g., SBA) comments were on a draft prior to revision for public release. Please consult the full interagency review comments in the EPA docket.

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"Comments from NIOSH identified three genotox studies – Chebotarev et al 1986, Vasudeva and Anand 1996, Yager et al 1986 - that are not included in EPA's evaluation, that provide experimental evidence supporting a genotoxic mechanism of toxicity for formaldehyde. While the first is in Russian, an English abstract is available, and for the other two they are available in English. If EPA is excluding all studies that are not in English, this is problematic and deserves some discussion and scrutiny." "NIOSH commenters also noted the failure to include an important published meta-analysis of myeloid leukemia risks in occupationally exposed workers, focused on occupations known to have high formaldehyde exposures by Zhang et al 2009. The study shows a statistically significant 1.5X increase leukemia in 15 studies (RR=1.54, CI 1.18-2.00), and an almost 2-fold higher risk for myeloid leukemia in six studies (RR=1.90, CI 1.31-2.76). Omission of this important paper should be corrected."	NRDC (2)	1	*Literature search and screening* EPA Note: 2 of the 3 noted studies are cited in the Appendices; the third is tagged in HERO. As described in the Handbook, IRIS staff consider the criticality of non-English studies (e.g., based on a translated abstract or review by a native speaker) with respect to their potential impact on assessment conclusions. Non-English papers considered unlikely to have a substantial impact, such as this one on a topic for which there are many studies, were not translated. Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.
"There are numerous studies that should have been evaluated in the Draft Assessment, but were not cited or referenced. EPA has excluded or dismissed a number of key studies, reviews, responses, and presentations, with a majority having been presented in correspondence and presentations by the ACC Formaldehyde Panel to the Agency since 2011."	ACC (0100; 8, 9, 20) ACC (0101-0102; 1) ACC (0103; 11)	1, 1a	*Literature search and screening; Responsiveness to NAS (2011); IRIS Handbook*

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"Routinely over the last decade, the Panel has met with and provided IRIS staff information on new scientific findings and publications related to the deficiencies identified in the NASEM review of the 2010 Draft IRIS Assessment of Formaldehyde. It is therefore unclear why many of these studies have not been included in the 2022 Draft Assessment after such longstanding outreach and communication with EPA on the part of the Panel. A representative sample of the engagements and communications with the EPA have been provided as attachments to this submission." "The 2022 Draft Assessment does not respond to NASEM's recommendation to clearly document its methods for study selection…As noted, systematic review methods have developed substantively since the NASEM 2011 review. The IRIS Handbook includes a highly detailed and structured process for literature search and selection. However, the process for inclusion and exclusion of studies from IRIS assessments, including formaldehyde, diverges from current best practices. For example, there are numerous places in the systematic review when EPA can choose to exclude studies without justification, including after refinement of the study plan or organization of the hazard assessment." "The 2022 draft Formaldehyde Review is not clear on the methods for study selection, and in some cases appears to deviate from best practices for systematic review, particularly for studies published between 2016 and 2021. Specifically, for the 2016-2021 studies, after comparing these studies to the PECO criteria, EPA assessed whether studies were "potentially impactful" - a subjective process to further narrow the body of evidence. EPA states this process relies on "expert judgment by two reviewers." Particularly concerning is that aspects of study quality assessment are intertwined in these criteria - for example, the criteria pertaining to animal studies with multiple dose levels. While multiple doses are preferred to evaluate dose-response relationships in animal toxicity studies, some single-dose studies may still be informative for critical endpoints or MOAs and therefore should not be excluded before full evaluation. Additionally, criteria related to selecting relevant mechanistic data are vague, with no guidance other than inclusion of only those "most directly related to the mechanistic uncertainties identified in the 2017 draft." The subjective selection of recently published studies is apparent in the failure to include numerous critical re-analyses and MOA assessments, as detailed in the comments submitted by ACC's Formaldehyde Panel." "The systematic review of literature contained in the Draft Assessment was inadequate. The Draft Assessment itself verifies that the systematic review was bifurcated and rushed, and that simple literature searches were performed pre-2017 and post-2017…The above indicates that, against EPA policy, a full systematic review of the literature was not conducted before release of the Draft Assessment for peer-review. Also, inadequate and incomplete science cannot be	ACC (0083a; 4)		EPA Note: the HERO database was used to document study screening decisions.

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justified by a desire to "expedite" an update to a 12-year-old draft document. This deficiency must be addressed before any further revisions are initiated." "The criteria for inclusion/exclusion of studies published after 2017 are unclear. The Draft Assessment gives the appearance of subjectively excluding evaluation of any studies that did not impact conclusions made before 2017, in confidential internal review drafts that remain unavailable to the public and were not externally peer-reviewed." *[Please see docket for details and supporting information]*			
"The EPA also disregarded the Mundt et al. (2018) summary of relevant studies [Meyers et al. 2013; Coggon et al. 2014; Talibov et al. 2014; Saberi Hosnijeh et al. 2014] published in the 6 years following the NRC review of EPA's Draft IRIS Toxicological Review of Formaldehyde and addressing several gaps identified by the NRC...EPA's characterization of the literature published since the 2010 IRIS draft is limited and would have been informed by the summaries provided in Mundt et al. (2018)." "I reviewed the recently released IRIS Toxicological Review of Formaldehyde-Inhalation (External Review Draft, 2022) to assess the accuracy and completeness of my formaldehyde research publications. Specifically, I identified all occurrences of citations to my publications in each of the IRIS documents (Main Text, Overview document, and Supplementary Materials), then evaluated the presentation of the information (i.e., risk estimates) and the interpretation of these publications. As detailed further below, I have published 18 formaldehyde publications, but the Draft only cites 10. Several of the omitted papers were critical contributions to the literature on the potential human health effects of formaldehyde. Additionally, in several instances, EPA has mis-interpreted and mis-cited my publications in a manner that substantively affects the interpretation of these individual studies and the overall weight of the evidence regarding formaldehyde carcinogenicity. EPA should consider re-reviewing all 18 publications and updating the Draft to add missing studies, correct citation errors, and revise the language characterizing the findings of these studies." *[Please see docket for details and supporting information]*	Cardno (0095; 5) Cardno (0082; 1)	1	*Literature search and screening* EPA Note: the primary studies indicated here are cited in the draft. Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.
"The Draft Assessment often relies on animal studies performed with novel and unvalidated test methods to reach conclusions. As an example, as described further in these peer-review comments, each of the animal studies relied upon for developing organ specific reference concentrations (osRfCs) in the Draft Assessment, relied on novel methods, such as measuring seminiferous tubule diameter, without providing any hematoxylin and eosin (H&E) stained tissue section histopathological evaluation by a trained pathologist, or measuring metal	ACC (0100; 26, 35, 42) ACC (0083a; 4, 6, 7) ACC (0103; 21, 22)	1a	*Study evaluation; Responsiveness to NAS (2011); IRIS Handbook* EPA note: study evaluation methods

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concentrations in lungs or testes without even providing critical information such as body weights, food consumption, hematology, clinical signs, sufficient number of animals for statistical evaluation, etc. as is expected of any well conducted toxicology study using validated endpoints for assessing toxicity." "A critically deficient evaluation domain for the assessment of formaldehyde is methanol co-exposure. Any study (epidemiological or animal) with methanol co-exposure should generally be classified as uninformative rather than "low confidence" when related to systemic effects. The Draft Assessment overstates in their conclusions "...the evidence indicates that inhalation of formaldehyde likely causes increased risk of xxx" for studies that were confounded by methanol." "Epidemiology studies without any analytical sampling should have been excluded from the determination of hazard and/or dose-response...Below is an example of an epidemiology study, Taskinen et al. (1999), that was graded with medium confidence. This paper should not have been carried forward due to multiple deficiencies, including a lack of analytical data (Table 1-58, p. 1-415)" "The study quality assessment framework used in the 2022 draft appears different from that described in the Handbook, allows for significant reviewer subjectivity, and ultimately is unclear on how confidence classifications were determined. The depiction of EPA's evaluation of study confidence process (Figure II) is convoluted, and the study evaluation tables (e.g., Appendix Tables A-105 and A-106) that summarize results of individual studies are difficult to read and interpret." "Further, the EPA approach to study quality assessment focuses on three areas: (1) reporting quality, (2) risk of bias, and (3) study sensitivity, but primarily emphasizes risk of bias. Certain categories are more important to judging study quality than others. For example, exposure characterization is a critical evaluation domain for epidemiological studies, including the formaldehyde literature, which is plagued by studies with poor surrogates for exposure (e.g., studies relying on next of kin reporting embalming practices of deceased workers). The 2022 draft includes a lettered "grading" system for exposure assessment; this system, which is poorly described, does not appear in the Handbook or in any other agency study evaluation framework. Additionally, risk of bias is only one facet of internal validity (bias reflects a systematic error only, while internal validity is also impacted by other non-systematic errors)." "Overall, EPA does not sufficiently address the NASEM recommendations relating to evaluating the quality and reliability of individual studies and must improve this in their general approach to study quality evaluation. EPA should revisit its framework for evaluating exposure assessment in epidemiological studies of formaldehyde exposure and revise its process for			and decisions are explained in Appendix A.5 (documentation emphasizes major study limitations that drive confidence ratings lower).

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evaluating mechanistic information to ensure it is a uniform and reproducible methodology across endpoints. EPA should consider aligning with the exposure characterization domain within the data quality evaluation framework developed for Toxic Substances Control Act (TSCA) risk evaluations. "The 2022 Draft Assessment conclusions are speculative and lack scientific confidence because EPA applied a flawed and subjective study evaluation method, especially in the analysis and interpretation of the epidemiology data...While EPA has made progress in this area, the study evaluations presented in the 2022 Draft Assessment need improvement and reflect two distinct but related issues: 1) several important deficiencies remain in the evaluation framework provided in the IRIS Handbook and 2) the 2022 Draft Assessment fails to follow the IRIS Handbook." "The 2022 draft incorporates a defined methodology and detailed discussions of mechanistic and MOA information for some endpoints, but not others. The Supplemental Information details a set of criteria for judging the strength of the evidence for mechanistic events associated with non-cancer respiratory effects (Table A-64). The draft also provides evidence tables summarizing general study characteristics and findings for mechanistic studies of respiratory effects. The ''utility and notes' column provides the overall confidence rating for that study; however, details on the rating are provided only for some low confidence studies." "EPA's analysis and interpretation of epidemiology data in the 2022 Draft Assessment is flawed. Not only does the study evaluation framework deviate from that required in the IRIS Handbook, but also EPA does not clearly communicate the results of its study evaluation. EPA also fails to consistently apply its own IRIS rating system for the robustness of exposure categorization, fails to thoroughly consider exposure latency, implements a highly subjective methodology for evaluating study reporting, biases, and sensitivity, and selectively interprets studies according to particular exposure metrics. All of these oversights lead to a lack of confidence in EPA's conclusions. Specific issues are described in detail below." *[Please see docket for details and supporting information]*			
"The IRIS Draft significantly underestimated the impact of co-exposure on the confidence in assessing how formaldehyde may lead to leukemia and associated mechanistic events in both experimental animal models and humans...The results [Lu, Gu, et al. 2012] strongly indicate that studies confounded by methanol in exposure should be excluded from any rigorous risk assessment of formaldehyde. The EPA IRIS Draft acknowledges that methanol may influence the confidence of assessment by stating 'although results may be confounded by methanol co-exposure (low confidence).' However, the EPA IRIS Draft still used these studies to support several hypothesized mechanistic events associated with formaldehyde induction of	UNC (31-34)	1a	*Study evaluation*

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lymphohematopoietic cancers." "Recommendation: The EPA IRIS Draft needs to discuss how methanol co-exposure significantly impacts evidence-based risk assessment of formaldehyde. Any study, including epidemiology studies, with potential methanol co-exposure should be excluded from the integration of evidence, as methanol seriously confounds the finding and potential understanding of mechanistic events." *[Please see docket for details and supporting information]*			
"EPA should evaluate carcinogenicity entirely under its 2005 Guidelines for Cancer Risk Assessment (2005 Guidelines). The 2005 Guidelines and descriptors have not been harmonized with the re-purposed GRADE framework and descriptors used in the IRIS Handbook." "The 2022 Draft Assessment must comply with EPA's guidelines for carcinogenic risk assessment…In implementing its Information Guidelines, EPA relies on existing guidelines and policies, which includes EPA's Guidelines for Carcinogenic Risk Assessment (Cancer Guidelines). The Cancer guidelines explicitly note that 'when judging and considering the use of any data, the basic standard of quality, as defined by the EPA Information Quality Guidelines, should be satisfied." "Thus, the 2022 Draft Assessment fails to rely on the best available science and apply a transparent and systematic review incorporating a weight-of-evidence approach that properly integrates evidence streams in assessing potential non-cancer and cancer risks of formaldehyde exposures, especially at human relevant, low levels of exposure. Moreover, EPA repeatedly cites its Cancer Guidelines but fails to properly apply them. As a result, EPA's linear unit risk estimate for NPC is essentially unchanged from the value derived over 30 years ago, despite the prodigious growth in the scientific database on formaldehyde indicating that formaldehyde is a threshold carcinogen." "The Draft Assessment often states the assessment followed EPA's Cancer Guidelines (U.S. EPA 2005), without citation. Likewise, there is no discussion of rationale for departing from the Guidelines when it did." "Regarding evidence synthesis and integration within and across lines of evidence, the 2022 draft Formaldehyde Review does not follow best practices for systematic review. Perhaps most importantly, there is a greater reliance on "strength" rather than "weight" of evidence. For example, the draft concludes that that the strength of the human evidence for myeloid leukemia is "robust" based on "several" studies with consistent findings. EPA's conclusion is based largely on the Beane Freeman analyses of the NCI cohort (pg. 1-542). EPA did not appropriately integrate apparently conflicting findings in the older epidemiological studies (Hauptman et al. (2009) funeral workers study, Beane Freeman et al. (2009) analysis of the NCI cohort) with the analyses published more recently, which demonstrate no excess in cancer risk	ACC (0083b; 2) ACC (0083a; 6-7) ACC (0100; 26, 68) ACC (0103; 1, 7, 8, 9, 14, 17, 20)	1a, 1b	*Evidence synthesis and integration; Responsiveness to NAS (2011)* EPA Note: Interagency reviewer (e.g., ATSDR) comments were on a draft prior to revision for public release. Please consult the full interagency review comments in the EPA docket.

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(e.g., Checkoway et al. (2015) re-analysis of the NCI cohort). EPA should re-examine its evaluations of study confidence (and risk of bias, especially including statistical analyses) and more fully integrate and interpret the earlier studies in the context of the broader body of more informative and updated studies." "Strength and weight of the evidence determinations in animal studies are often subjective, unfounded, and contradictory." "EPA's treatment of mechanistic data continues to be problematic. As EPA notes on page xxxviii, "the lack of mechanistic data explaining an association did not discount results from human or animal health effect studies." While very strong, consistent and positive evidence in animals and humans, indicative of an effect, is often sufficient to make some conclusions on the likelihood of human health risk, in most cases, there is some inconsistency both within and across the animal and human streams of literature, which makes mechanistic information exceedingly important. EPA should give more weight to mechanistic information, particularly when it exists and does not support a human-relevant mechanism. The Agency for Toxic Substances and Disease Registry (ATSDR) echoed this concern in their interagency review comments." "The 2022 Draft Assessment fails to incorporate a weight of evidence approach or properly integrate evidence streams in assessing non-cancer and cancer endpoints." "The 2022 Draft Assessment does not incorporate best practices for evidence synthesis…The process of evidence synthesis (within lines of evidence) and evidence integration (across lines of evidence) are critical but still somewhat underdeveloped areas of systematic review. In the 2022 Draft Assessment, the procedure is described, but only in general terms, as depicted in the figure below (a figure that is found in the 2022 Draft Assessment but does not appear in the IRIS Handbook). Further, it is notable that there is no discussion of mechanistic studies or information on MOA." "The 2022 Draft Assessment does not incorporate best practices for evidence integration. In 2011, NASEM gave the following recommendation (in this case, in regard to the lymphohematopoietic malignancies): As stated in EPA's cancer guidelines, EPA's approach to weight of evidence should include 'a single integrative step after assessing all of the individual lines of evidence.' Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version." "NASEM (2011) went on to criticize the 2010 Draft Assessment for the lack of a clearly articulated framework for establishing causation on the 'basis of the weight and strength of the			

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evidence.' EPA reports that it implemented NASEM's recommendations by evaluating studies related to each endpoint using "a common evidence integration framework for determinations of causality" with rationales described in the integrated summaries of evidence (Appendix D of the 2022 Draft Assessment). Indeed, EPA has developed a framework for weighing evidence, informed by Bradford Hill postulates (as recommended by NASEM 2011) as presented in the IRIS Handbook and the 2022 Draft Assessment. However, as applied, the integration process requires substantial scientific judgment, and the 2022 Draft Assessment does not clearly describe the way in which evidence was synthesized and integrated to reach its determinations of causality." *[Please see docket for details and supporting information]*			
"Regarding the assessment of the weight of evidence (i.e., evidence integration), NRDC strongly supports EPA's reasoned approach regarding mechanistic information, stating that mechanistic events and associations are preferred, but that, "the lack of mechanistic data explaining an association did not discount results from human or animal health effect studies" (p. 38). To that end, NRDC disagrees with the comment from ATSDR, arguing that the lack of mechanistic information should be treated not as a data gap, but as a "reason to down-grade the evidence findings. NRDC supports EPA's determination that, "Mechanistic understanding is not a prerequisite for judging the evidence, and thus absence of knowledge should not be used as a basis for decreasing strength NTP (2015); NRC (2014a). The human relevance of animal findings is assumed unless there is sufficient evidence to the contrary [see IARC (2006); U.S. EPA (2005a)]." (p. 40) This is also consistent with the IARC Preamble, updated January 2019 following a global process of public comment and scientific peer review. EPA could update the IARC reference in the text."	NRDC (3)	1	*Evidence synthesis and integration*
"NASEM has provided several recommendations regarding the development of toxicity values, including that toxicity values should be more representative of the body of evidence, and should use formal methods for combining multiple studies. It is critical that EPA address NASEM recommendations regarding developing toxicity values to better reflect the state-of-the-science in this field and demonstrate how the systematic review process informs the development of the values." "Subjective exclusion of "evidence against" (not supporting) the conclusions reached in the Draft Assessment is contradictory to EPA guidelines…The Draft Assessment, however, sets aside both animal and mechanistic information and solely calculates Reference Concentrations (RfCs) and Inhalation Unit Risks (IURs) based on individual study results. Toxicokinetic, dosimetry, animal, and mechanistic data are not integrated into the assessment of epidemiology results	ACC (0083a; 7) ACC (0100; 21)	1a, 2	*Dose-response analysis; general (toxicokinetics)*

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when calculating exposure limits/IURs, when they appear to contradict numerically identified associations from epidemiology." *[Please see docket for details and supporting information]*			
Charge Question 2: Toxicokinetics			
"ATSDR also stated that EPA's assumptions regarding the toxicokinetics of formaldehyde exposure used to develop systemic reference concentrations '…doesn't make any sense' and that EPA should examine confounding toxicities 'before making any evidence conclusion for formaldehyde.'"	USCC (4)	2	*General (toxicokinetics)* EPA Note: Interagency reviewer (e.g., ATSDR) comments were on a draft prior to revision for public release. Please consult the full interagency review comments in the EPA docket.
"U.S. EPA failed to respond to the spirit of the NRC's comments on U.S. EPA's 2010 draft formaldehyde assessment as it relates to toxicokinetics and MOA analysis." *[Please see docket for details and supporting information]*	ToxStrat (7)	2	*General (toxicokinetics)*
"EPA's presentation of the toxicokinetics – including the considerations of endogenous formaldehyde – is generally well-reasoned and well-presented."	NRDC (4)	2	*Endogenous formaldehyde*
"First, exogenous and endogenous formaldehyde are not similar -- they are identical. Claiming that there are no specific data indicating that they are different implies a conclusion that is not correct. While there are no data indicating that they are different, there is overwhelming evidence that formaldehyde is simply formaldehyde, regardless of where it is found or how it is generated. Secondly, stating that "the rate of cellular detoxification of exogenous formaldehyde remains unknown" ignores the wealth of data on the half-life of formaldehyde in vivo and its non-specific binding to electrophilic centers, as well as an abundance of data on the kinetics of detoxification by glutathione and aldehyde dehydrogenase. Thirdly, one of the best characterized metabolic pathways is the one-carbon pathway that includes detoxification of formaldehyde by formaldehyde dehydrogenase (ADH5/GSNOR). Stating that "our understanding the contribution of endogenous formaldehyde is minimal" ignores the extensive database demonstrating that formaldehyde is an essential anabolic building block needed for normal metabolism. Simply, one cannot live in the absence of formaldehyde. Ignoring the essentiality of formaldehyde and the equivalence of formaldehyde regardless of its origin is a fundamental flaw of the Draft Assessment. When in a state of homeostasis, there is no added	ACC (0100; 29--31)	2, 1a	*Preface; Endogenous formaldehyde; Toxicokinetics*

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risk. As such, assessing added risk in the context of homeostasis must be a critical component of the Draft Assessment and must not be put aside. Key to understanding and managing exogenous inhaled formaldehyde is that at concentrations that do not upset normal variability (i.e., ≤1-2 ppm) in metabolic processes, there is no added risk. The Draft Assessment must be revised to integrate relative dosimetry and define concentrations at which inhaled formaldehyde does not upset normal homeostasis. This topic was also the focus of the "bottom up" approach published by Drs. Swenberg, Starr and Lu in several peer-reviewed publications, which were incorrectly characterized in the Draft Assessment." "The Draft Assessment concludes that an understanding of homeostasis is not important when considering if there is added risk from exogenous exposure to formaldehyde. However, it is critical to understand the normal role of formaldehyde in the body, such as its central role in one carbon metabolism when determining adversity. The Draft Assessment also speculates that inhaled formaldehyde is somehow different than endogenously produced formaldehyde, an assumption that challenges our basic understanding of chemistry. Formaldehyde is a simple molecule; it is simply formaldehyde and should not be assessed differently or separately, depending on whether it is generated in the body or derived from an external source." "While the previous assessment and the current assessment provide a discussion of formaldehyde toxicokinetics, the 2022 Draft Assessment does not provide a discussion or consideration of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations, as recommended by NASEM.[79] This evaluation is critical in drawing conclusions regarding the potential for health effects following inhalation exposure of formaldehyde…Formaldehyde is a classic example of a chemical for which the beneficial and adverse effects can only be considered in the context of dose-dependent transitions. Endogenous formaldehyde is essential to life while high exogenous concentrations result in adverse effects. There are numerous studies that provide evidence that exogenous formaldehyde does not move past the portal of entry in multiple species (i.e., rats and non-human primates) following both acute and subchronic inhalation exposure across a range of air concentrations (0.001 ppm to 15 ppm) Kleinnijenhuis et al. 201382; Lu et al. 201083, Lu et al. 201184; Edrissi et al. 201385; Moeller et al. 201186; Lai et al. 201687; Yu et al. 201588; Leng et al. 201989)… Despite decades of research using highly sensitive methods, EPA continues to derive a risk for myeloid leukemia in the absence of even a hypothesized MOA and with clear toxicokinetic evidence that formaldehyde does not move beyond the portal of entry." "It is clear that toxicokinetic considerations are key to integrating the multiple streams of evidence necessary to make a sound data-driven conclusion. However, for leukemia, the Draft Assessment disregarded the wealth of information available that demonstrates that inhaled			

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formaldehyde is not systemically distributed as well as dosimetry related to the naturally occurring background tissue concentrations of formaldehyde. Instead, the Draft Assessment relied on pure speculation to support what was apparently a pre-determined outcome. Notably, there is not one place in the Draft Assessment where the evidence against there being a mechanism of LHP carcinogenesis following inhalation exposure to formaldehyde is objectively discussed." *[Please see docket for details and supporting information]*			
"Since the NAS (2011 review), numerous studies have conclusively demonstrated that inhaled formaldehyde is not systemically circulated through the blood or other systems. Furthermore, there is now direct molecular dosimetry evidence that, at concentrations below 15 ppm, there is no detectable systemic delivery of inhaled formaldehyde, at detection limits over a thousand times lower than endogenous levels of formaldehyde. The Draft Assessment, however, fails to take this evidence into account and incorporate the recommendations of the NAS (2011) peer-review by developing RfCs for reproductive and developmental effects (Table 2-10) that rely on the assumption of systemic delivery of inhaled formaldehyde." "Over the last four decades, toxicokinetic and toxicodynamic studies have consistently demonstrated a lack of systemic distribution of inhaled formaldehyde concentrations up to 15-20 ppm when directly measured in tissues (Heck et al., 1985; Casanova et al., 1988). More recent publications quantified protein and DNA biomarkers of formaldehyde exposure confirming that there is no systemic distribution of formaldehyde air concentrations ≤15 ppm (Lu et al. 2010, 2011; Edrissi et al. 2013, 2017; Yu et al. 2015; Lai et al. 2016; Leng et al. 2019)." "Data from multiple sources provide strong evidence that formaldehyde is not systemically distributed and, therefore, could not directly cause any systemic effect. The Draft Assessment assumes that formaldehyde acts via an unknown pathway to elicit systemic effects (e.g., female reproductive or developmental toxicity, male reproductive toxicity, nervous system toxicity, and leukemia)." *[Please see docket for details and supporting information]*	ACC (0100; 27, 28, 34)	2, 4, 5	*Distribution*
Charge Question 3: Respiratory System Noncancer Health Effects			
"The 2022 Draft Assessment gives equal weight to all the study designs, and simply attributes the variation seen as part of human variability. EPA does not appear to acknowledge that subjective measures can easily be influenced by other factors such as odor perception (Cometto-Muñiz and Cain 1991; Brüning et al., 2014). Six studies were considered for derivation of Points of Departure (PODs) (Hanrahan et al., 1984; Kulle et al 1987; Anderson and Molhave 1983; Liu et al, 1991; Mueller et al., 2013; Lang et al 2008), but only three (Andersen and Molhave, 1983; Hanrahan et al., 1984; Kulle et al 1987 –all medium quality as assessed by EPA,	ACC (0103; 59-60, 63) ACC (0100; 4)	3, 5	*Sensory irritation*

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where Andersen and Molhave 1983 was a chapter as opposed to a peer-reviewed publication) were considered for POD derivation in spite of higher quality studies (Lang et al., 2008; Mueller et al., 2013) being available. (Lui et al 1991 was also considered medium quality.)...given the stronger quality of these studies [Mueller et al. 2013 and Lang et al. 2008], RfCs could have been derived from NOELs." "EPA inappropriately dismisses carefully designed chamber studies [Mueller et al. 2013 and Lang et al. 2008]." "From the authoritative assessments and reviews published prior to 2019 (ANSES 2018, 2019; Danish Ministry of the Environment 2014; ECHA 2016, 2019; SCOEL 2016; EPA 2008, 2010; WHO 2010), there is a consistent identification of the Lang et al. (2008) and Mueller et al. (2013) studies as key for defining the most sensitive endpoints from which to derive acceptable concentrations of formaldehyde following acute/short-term inhalation exposures. The authoritative bodies identified these two studies because they are high-quality studies, where exposure concentrations were known and controlled, exposures were randomized and double-blinded, and individuals served as their own controls. They noted the studies included both subjective and objective measures, and individuals who were identified as being hyper- or hyposensitive to the effects of formaldehyde. Importantly, there is no evidence indicating an increased sensitivity to sensory irritation to formaldehyde among people often regarded as susceptible (asthmatics, children, and older people) (WHO 2010)." "The Draft Assessment sets aside the controlled human chamber studies, in conflict with NAS (2011) recommendations." *[Please see docket for details and supporting information]*			
• "EPA's reliance on residential or home studies is misguided and is not the Best Available Science • EPA should rely on human volunteer chamber studies that have proper controls to reduce or eliminate confounding factors and false positives • EPA fails to rely on Mueller et al. 2013 and Lang et al. 2008, that are considered by many countries as 'critical studies' (e.g., France, Netherlands, 2019) • EPA's representation of the sensory irritation studies as an adverse health effect cannot be considered the best available science." *[Please see docket for details and supporting information]*	AFPA (0073; 7)	3a	*Sensory irritation*
"Formaldehyde has a pungent odor that can be sensed at low ppb levels in air and which at higher concentrations can elicit the onset of sensory irritation; both serve as a warning system of exposure. The lowest potentially undesirable effect levels in humans are generally recognized as odor detection via the olfactory nerve (CN I), resulting in decreased air quality,	MCSC (1, 4, 5, 14-15)	3	*Sensory irritation*

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and following that, eye and nasal tract chemosensory stimulation (i.e., chemesthesis)[1]. Chemesthetic detection of formaldehyde occurs via cutaneous nerve fibers in the eye and mucus membranes in the nose, via the trigeminal nerve (CN V). This ability to detect formaldehyde or any pungent chemical in the ocular and nasal mucosa represents a normal sensory physiological process and is not tissue irritation (i.e., an inflammatory response) nor an adverse health effect." "Olfactory and chemesthetic detection of formaldehyde can prompt adaptive responses such as preference for mouth vs nasal breathing to reduce unpleasant odor or responses such as eye blinking. However, these sensory responses occur from neuronal stimulation, and are therefore not precursors to an adverse health effect. In contrast, tissue irritation that is related to formaldehyde binding to macromolecules, including protein-protein cross-linking, in nasal epithelial cells, resulting in tissue damage and inflammation is adverse. The differing mode of action for nasal chemesthesis vs nasal tissue irritation represents the difference between a sentinel vs a precursor effect." "From a regulatory viewpoint, the continuum of effects associated with increasing formaldehyde air concentrations can be broken down into a definable sequence: 1) at low concentrations, odor detection and/or sensory chemesthesis or other sensory detection (NOAEL); 2) at higher concentrations, uncompensated upper respiratory tract tissue irritation (the first adverse or critical effect, LOAEL); 3) at yet higher concentrations, cytotoxicity and regenerative hyperplasia (AEL); and 4) at the highest concentrations, potentially nasal tumors (FEL). Consequently, it is important to determine the concentration(s) of formaldehyde that can reliably be associated with non-adverse warning properties such as odor detection and chemesthesis, as well as concentrations objectively causing adverse tissue effects such as cytotoxicity and inflammatory responses." "There is substantial inconsistency in how participant demographics are assessed. The PODs which could be derived based on two considered controlled human exposure studies were rated with less confidence because the study participants were young, healthy volunteers. The more robust studies by Lang et al and Mueller et al (Lang, Bruckner et al. 2008, Mueller, Bruckner et al. 2013) were dismissed for these same reasons and because the USEPA found it 'difficult to define an adverse response level cutoff for either objective or subjective symptom scores' (Table 11, p35). However, according to the Hanrahan et al study, "negative coefficients for respondents age were found to be significant for both ocular irritation models, indicating a higher report prevalence in younger persons"(Hanrahan, Dally et al. 1984). The well-established declines in olfactory and trigeminal (chemesthetic) sensitivity with age and age-related diseases means a younger, healthier population (which is typically the demographics of			

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participants in controlled exposure studies) will be most sensitive to the odor and irritancy of formaldehyde (Doty, Shaman et al. 1984, Doty 1989, Wysocki, Cowart et al. 2003)." "The Draft Document also marginalizes controlled exposure studies for excluding smokers, perhaps assuming that this is a sensitive subpopulation that should be included. However, smoking decreases the sensitivity of the cornea and conjunctiva (Thomas, Jacob et al. 2012) and smokers' show reduced nasal/ocular sensitivity to many irritant chemicals (Cometto-Muñiz and Cain 1982, Dunn, Cometto-Muñiz et al. 1982), thus it is appropriate to exclude them in a controlled exposure study where the critical endpoint is sensory irritation. As well, asthma and other health conditions are not considered to predispose individuals to be more sensitive to formaldehyde. Thus, the concerns raised about the populations tested in these well-conducted controlled exposure studies are without merit." *[Please see docket for details and supporting information]*			
"The Draft Assessment did not present an alternative to the RfC based on Krzyzanowski et al. (1990), as directed by the NAS (2011) and does not address the inherently limited reliability of the cross-sectional study design of the study and classified the study confidence as 'high.'" "These contradictions and "plausible" speculations do not inform an evidence-based assessment. If there is no dose-response, not time concordance, and no mode of action for the observed effects, no pathological basis for the effects, and no distribution to the [lower respiratory tract], there is no support for any cause-and-effect relationship. The Draft Assessment would be improved by simply stating the evidence for and against causal association, without speculation about plausibility of undefined causes." *[Please see docket for details and supporting information]*	ACC (0100; 3, 71)	3b	*Pulmonary function; Responsiveness to NAS (2011)*
"EPA's integration of evidence is overly simplistic. Asthma is widely recognized as a heterogeneous group of diseases based on clinical features, physiological characteristics, and varying outcomes ranging from mild to severe. Variation in response to different asthma treatments also suggests that there are multiple mechanisms and pathways that are relevant to the development and exacerbation of asthma. It is not a single disease entity. EPA does not adequately address potential differences in asthma phenotypes that likely represent different underlying biological mechanisms for asthma development. EPA does not describe how the postulated mechanistic pathways are potentially related to different asthma phenotypes. There is a large body of ongoing research focused on improving the understanding of the specific biological mechanisms (or endotypes) that are associated with phenotypes (for example, see Akar-Gibril et al. 2020; Berdine et al. 2020; Carr et al. 2018; Kuruvilla et al. 2019; Kaur and Chupp 2019; Conrad et al. 2021; Schoettler and Strek, 2020; McDowell and Heaney 2020; Lötvall et al. 2011; Wenzel et al. 2012). As a result of differences in phenotypes and endotypes,	ACC (0103; 66-67, 69) ACC (0100; 3)	3d, 5	*Prevalence of current asthma and degree of asthma control* EPA Note: the meta-analysis results are presented in Figure 1-9 of the draft Toxicological Review.

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there are likely different mechanisms (and different modes of action) by which formaldehyde could potentially increase risk. At the very least, the evidence related to potential mode of action should be synthesized separately for occupational asthma (a phenotype that is generally not related to atopic or allergic asthma). Differences in potential mechanisms and the pathogenesis for early onset/atopic asthma versus early onset/non-atopic asthma could also be described (even if these groups cannot be distinguished in the existing epidemiologic studies). Collectively, these differences, which are not related to differences in exposure concentrations, potentially explain inconsistencies in results." "Two studies were selected to derive a point of departure (POD) for current asthma (Annesi-Maesano et al. 2012; Krzyzanowski et al. 1990); however, neither study showed clear associations between current asthma and formaldehyde exposure…Two studies were selected to derive a POD for poorly controlled asthma (Dannemiller et al. 2013) and Venn et al. (2003). These studies only reported correlations between formaldehyde concentrations and poorly controlled asthma. Both studies were cross-sectional studies that relied on response to questionnaires for the identification of poorly controlled asthma. Neither study controlled for potential confounding by indoor allergens that trigger asthma." "EPA's misrepresentation of the two studies (Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012) it relied on to derive a POD cannot be ignored. EPA's bias against the chemical to even use a negative study in support of an association does not represent the best available science." "Not only did EPA ignore the two relevant publications by Drs. Golden and Holm, the 2022 Draft Assessment also ignored evidence on the key substances [acrolein] that are considered causally related to asthma. In doing so, the 2022 Draft Assessment presents conclusions that are at complete odds with NASEM (2000) (an authoritative review for the endpoint of asthma) and Kanchongkittiphon et al. (2015) (a comprehensive update involving 69 additional studies focused on indoor environmental exposures and exacerbation of asthma), both of which demonstrated a practical weight of evidence approach…EPA must therefore revise the 2022 Draft Assessment to include a practical Weight of the Evidence evaluation on asthma using the best available science and must account for the contributing role of acrolein." "The revised assessment does not provide clear criteria for evaluating evidence on asthma and provides insufficient support for the classification of formaldehyde as a asthmatogen. The Draft Assessment then calculates several RfCs based on asthma effects (Tale 2-10) without addressing the fundamental issues raised during the NAS (2011) review." "The 2022 Draft Assessment also appears to contain errors in the text:			

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• The 2022 Draft Assessment states that the EPA conducted a meta-analysis to calculate a summary effect estimate for similar results; there is no further information, and no summary effect estimates are reported. • Figure 1-11, Panel C: Effect Modification of Prevalence of Current Asthma in Children by Atopy Status) shows increased risks (odds ratios > 3.0) for both atopic and non-atopic asthma in the highest exposed group (>0.06 mg/m3, which also appears to be mislabeled as µg/m3). These odds ratios do not match the results presented in Annesi-Maesano et al (2012). Annessi-Maesano et al. (2012) reported odds ratios of 0.96 and 0.82 for the prevalence of current asthma in the highest exposed group for atopic children and nonatopic children, respectively." *[Please see docket for details and supporting information]*			
"...For the endpoint of asthma there is an authoritative review (NAS 2000) and a comprehensive update (Kanchongkittiphon et al. 2015) involving 69 additional studies focused on indoor environmental exposures and exacerbation of asthma...Having ignored these two relevant and knowledgeable publications, EPA has ignored evidence on the key substances that are considered causally related to asthma. In doing so, the Review presents conclusions that are at complete odds with NAS and Kanchongkittiphon, both of which demonstrated a practical Weight of the Evidence approach...Importantly, EPA provides a review of a subset of the relevant literature instead of a full Weight of the Evidence evaluation on asthma and allergy, when compared to the two reviews mentioned above and reaches a very different conclusion on the role of FA and asthma. EPA concludes that the "evidence indicates" a role of FA with "allergic conditions and current asthma symptoms or degree of asthma control" while the National Academy of Sciences and Kanchongkittiphon et al. (2015) find only limited or suggestive evidence of an association between FA exposure and exacerbations of asthma...Due to its incomplete review of the literature, this Review does not raise to the level of "Weight of the Evidence" using the "Best Available Science" as required by the Lautenberg amendments to the Toxic Substances Control Act (TSCA) (2016). As TSCA will rely on the Review to inform the Risk Evaluation we feel it should be required that EPA conduct a suitable review at this stage in the TSCA Risk Evaluation process. We also urge EPA to revise the document to reflect appropriately the conclusions of the current literature. Of note, the evidence provided in a recent paper (Golden and Holm 2017) that was not cited or integrated into the Review supplies a roadmap of why unrecognized exposure to acrolein is an important confounding factor in many indoor air-related studies focused on FA."	AFPA (0073; 2-7)	3d	*Prevalence of current asthma and degree of asthma* EPA Note: Formaldehyde-specific reviews and other studies with no primary data are considered as supplemental materials and tracked in HERO.

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"The above noted substances [acrolein] potentially present in indoor air that can exacerbate childhood asthma, many with different levels of certainty, present a substantial challenge with respect to designing and interpreting studies. The discovery that acrolein, an aldehyde that is 200 times more potent as a sensory irritant than FA (Fowles and Dybing 2003) and ubiquitous in indoor air, was significantly associated with asthma, whereas FA was not (Annesi-Maesano et al. 2012). Since it is plausible that FA has served as an unrecognized proxy for acrolein in studies conducted to date, our review (Golden & Holm, 2017) summarizes the well-established dose–response aspects of FA-induced irritation and its potential to exacerbate asthma symptoms. This is followed by a discussion of the available data on acrolein in sufficient detail to document its likely role in exacerbating asthma due to its irritant properties. The implications of acrolein as a previously unrecognized confounder are that indoor air studies, which report associations between FA and childhood asthma, should be interpreted with caution unless/until potential contributions and/or associations with acrolein are also considered. Even Annesi-Maesano et al, 2012, who EPA uses their data to provide a POD for "current asthma prevalence" stated, "Although small, the significant correlations between EIA and PM2.5 and acrolein represent an important message for public health as between 40% and 90% of people with asthma usually have EIA and could be at even higher risk when exposed to air pollution." In addition, as noted by Leikauf (2002) due to ever-increasing acrolein emissions into the environment, acrolein as a direct irritant may increasingly become a health hazard in individuals with respiratory diseases such as asthma." "Acrolein sources in indoor air are similar to FA...Therefore, it is reasonable to conclude that there is a sound exposure-based rationale for better understanding the potential health impacts of acrolein, particularly as they might relate to sensory irritation and asthma. EPA must incorporate this rational information into their Review." "It is well documented (i.e., Garrett et al., 1998, 1999; Rumchev et al., 2002, 2004) that other substances in indoor air (e.g., VOCs and fungal spores) can cause and/ or exacerbate respiratory symptoms quite apart from FA. Consequently, it is likely inappropriate to conclude that the results reported by Krzyzanowski et al. (1990) can be unequivocally attributed to FA alone in indoor air. EPA has used this study published 32 years ago as "eligible for POD derivation for current asthma prevalence." Findings of this study (i.e., Peak Expiratory Flow Rate or PEFRs) are questionable in view of the low levels of FA found in the homes and at odds with controlled human studies where FA was the only variable (e.g., Lang et al., 2009). In addition, as in most studies of this kind, the lack of measurements of allergens or other chemical agents that may have been present in indoor air and possibly contributed to reported symptoms is a major confounder. Although the authors did report greater changes in PEFR in children than in adults,			

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the use of this measure does not confirm the presence or absence of asthma or bronchitis or that FA (or something else) was responsible for this finding. This is the only study suggesting differential effects in children versus adults, hardly a convincing basis for concluding that children are more sensitive to FA." "EPA also states in Krzyzanowski et al. (1990), (a study used by EPA to develop a POD for "current asthma prevalence") that an "increased prevalence of current asthma was seen in the highest exposure group in a categorical analysis." It is unclear what data EPA are relying on in making this statement. However, as noted in Table 4 of this paper there are three exposure ranges reported, <40 ppb; 41-60 ppb; >60 ppb. There is no dose response exhibited in the data presented and the prevalence rate for asthma in the highest concentration group for children exposed to FA but not to environmental tobacco smoke was 0. The authors report, "…the prevalence rates of current asthma diagnosed by a doctor were significantly increased in children living in houses with high FA levels in the kitchen, but only in those also exposed to ETS." (Emphasis added). ETS is considered in the Kanchongkittiphon et al., 2015, review to be causally related to exacerbations of asthma in children. This incomplete presentation of the available data even in the studies EPA relies on is inherent in the Review and shows EPA's bias in the presentation of data." "EPA stated that Annesi-Maesano et al. (2012), reported that FA was significantly associated with rhinoconjuctivitis at median reported FA levels of 21 ppb. However, these levels at which rhinoconjunctivitis (i.e., eye/nose irritation) occurred appear inconsistent with substantial data on dose–response aspects of FA-induced sensory irritation from controlled human studies reported by others. This endpoint is likely confounded by other causally associated substances in indoor air that were not measured in this study and not considered by EPA. This endpoint should not be considered causally related with FA and the study should not be used to derive a POD." "Importantly, Annesi-Maesano et al. (2012) reported that FA was not associated with asthma in this study. Acrolein was the only exposure significantly associated with both asthma (OR: 1.37, 95% CI: 1.14-1.66) and allergic asthma (OR: 1.41, 95% CI: 1.16-1.73) whereas NO2 was statistically significantly associated with asthma (OR: 1.18, 95% CI: 1.01-1.39). FA was statistically significantly associated only with rhinoconjunctivitis (OR: 1.41, 95% CI: 1.08-1.85) but not with asthma." "Comparing the actual data in the [Annesi-Maesano et al. 2012] paper show that for the high dose of FA there is an increase in rhinoconjunctivitis (1.19), a decrease in asthma in the entire sample population (0.90), a decrease in asthma in atopic children (0.96) and a significant decrease in asthma among non-atopic children (0.82). Yet, EPA has used this study to			

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incorrectly include a FA POD for current asthma prevalence. The use of this study to derive or support a Reference Concentration for FA is not consistent with the Best Available Science." *[Please see docket for details and supporting information]*			
Charge Question 4: Systemic (i.e., Nonrespiratory) Noncancer Health Effects			
"NRDC supports EPA's determination that inhalation of formaldehyde "likely causes" female reproductive or developmental toxicity in women – EPA's conclusion is supported by evidence in humans, including time-to-pregnancy (TTP) and spontaneous abortion risk. As NIEHS noted in its comments, "it is reasonable to conclude that female reproductive toxicity based on TTP (Taskinen et al. 1999) and spontaneous abortion (John et al. 1994, Taskinen 1994, 1999) is supported by epidemiological evidence" (NIEHS p. 6) EPA notes that "mechanistic evidence explaining such effects without systemic distribution of formaldehyde is lacking" (p. 54). However, NIEHS comments noted that, "it has been clearly demonstrated that formaldehyde is metabolized to formic acid" which is demonstrated to impair embryo viability and is linked to adverse developmental outcomes (NIEHS p. 6). NRDC agrees with NIEHS that the addition of this scientific evidence and proposed mechanism would strengthen EPA's evaluation. NIEHS identified this as a "Tier 1" necessary revision. Nonetheless, NRDC concurs with EPA that mechanistic information is not necessary, and a data gap or the absence of knowledge should not be used as a basis for downgrading the strength of evidence. (p. 40)"	NRDC (5)	4a	*Female reproductive or developmental toxicity* EPA Note: Interagency reviewer (e.g., NIEHS) comments were on a draft prior to revision for public release. Please consult the full interagency review comments in the EPA docket.
"The best available science does not support EPA's conclusions regarding formaldehyde and reproductive and developmental effects. The NASEM (2011) Committee stated that EPA did not provide a clear weight of evidence discussion to support its classification for reproductive and developmental toxicity and did not agree with EPA's conclusions…As discussed further below, EPA maintains a similarly strong conclusion regarding the reproductive and developmental evidence, despite the absence of new supportive sentinel studies published in the last decade or any plausible MOA." "The Draft Assessment incorrectly concludes that 'evidence indicates' that inhalation of formaldehyde causes increased risk of reproductive and developmental toxicity, and classifies it as a reproductive and development hazard. This is despite the statement (p. 1-414) that 'The primary basis for this conclusion is based on bioassays in rodents testing formaldehyde concentrations above 6 mg/m^3.' In drawing this conclusion, the Draft Assessment excludes both toxicokinetic considerations and relative dosimetry. This is in direct opposition to Globally Harmonized Classification and Labeling (GHS) guidance as well as EPA guidance on evaluating reproductive and developmental toxicity. First, inhaled formaldehyde is not distributed systemically, thus, it does not affect normal formaldehyde concentrations in reproductive or developmental organs/systems, so it cannot be a direct hazard. Secondly, any reproductive	ACC (0103; 69) ACC (0100; 31)	4a	*Female reproductive or developmental toxicity*

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effects were only observed under conditions of high toxicity in the dams, which does not trigger a Hazard Classification for reproductive effects, according to EPA guidelines or GHS. As such, it must not be classified as presenting a reproductive and developmental hazard." *[Please see docket for details and supporting information]*			
"The U.S. EPA's hypothesize MOA for male reproductive effects misses a critical alternative explanation. Modeling the serum testosterone data from Ozen et al. (2005) resulted in good fitting models with a BMDL1SD value of 0.21 mg/m^3 in agreement with U.S. EPA (data not shown). Interestingly, this POD is similar to that derived for bodyweight gain changes and testes (see above). A very quick literature search reveals that food restriction affects testes weight and serum testosterone levels in rats (Rehm et al. 2008). If the bodyweight gain changes reported in Ozen et al. (2002) were due to reduced feed intake, then the changes in testes weight and serum testosterone might be related to changes in bodyweight as opposed to formaldehyde toxicity per se. Notably, these effects all occur at about the same concentration—a possible indicator that they are in fact related to one another. This hypothesis seems as likely, if not more likely, than U.S. EPA's hypotheses about indirect mechanisms like inflammation, oxidative stress, and neuroendocrine disruption (see section 1.3.2 of the Toxicological Review). That the linkage between feed intake and these same markers of toxicity are not even considered by EPA is problematic. Notably, the Ozen et al. (2002) study that EPA scored as high makes no mention of feed or water consumption despite the significant decreases in bodyweight gain. This calls into question the overall thoroughness and quality of this study."	ToxStrat (19)	4b	*Male reproductive toxicity*
"Neurotoxicity and reproductive and developmental toxicity studies used for dose-response and/or hazard classification did not meet the criteria in USEPA guidance for the confidence ratings proposed in the Draft Assessment yet were advanced (sometimes even all of the way to RfC development)... The Ozen et al. (2002) and Ozen et al. (2005) subchronic rat studies were rated 'high confidence' studies and used to derive osRfCs for potential male reproductive toxicity in the Draft Assessment. Both studies had numerous deficiencies that would lead to a grade of 'uninformative' and thus not used for either hazard classification or dose-response assessment, as follows." *[Please see docket for details and supporting information]*	ACC (0100; 35)	4b, 4c	*Male reproductive toxicity; Nervous system toxicity*
"The 2022 Draft Assessment stated, 'Overall, conclusive of a nervous system health hazard in humans exposed to formaldehyde was not identified (i.e., suggestive evidence).' The finding of 'suggestive evidence,' however is at odds with EPA's acknowledgement of inconclusive evidence. Indeed, a critical review of the available evidence suggests that an 'inadequate' descriptor would be more appropriate for this endpoint... Given the lack of data for any	ACC (0103; 71-72)	4c	*Nervous system toxicity*

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postulated MOA and failure to demonstrate consistent effects across any endpoint, an integration judgment of 'evidence is inadequate' is more appropriate rather than the proposed 'suggestive' integration judgment for nervous system effects." *[Please see docket for details and supporting information]*			
Charge Question 5: Noncancer Reference Concentration (RfC)			
"It is difficult to verify all the BMD modeling results as Appendix B clearly indicates that the model outputs were run nearly a decade ago in January of 2013, apparently using EPA's BMD software (BMDS) v1.9. The current version of BMDS is v3.2. U.S. EPA's BMDS website (https://www.epa.gov/bmds) explicitly states that BMDS 2.7 is no longer supported, and this must also be true for prior versions. It is reasonable to expect that any new U.S. EPA assessment should use the most current (and supported) version of BMDS. The U.S. EPA should re-run all the BMD modeling in the assessment with the latest version of BMDS. Curiously, many of the BMD modeling results in this document are expressed in units of mg/kg-d as opposed to mg/m3. This is likely a result of the modeling software not knowing the units, but it is surprising that EPA did not correctly indicate the units. Moreover, all the discussion about BMD models should technically be benchmark concentration (BMC) as these are inhalation concentrations as opposed to oral doses." "U.S. EPA's benchmark dose modeling of rat respiratory histopathology has several reporting and methodological flaws." "U.S. EPA's benchmark dose modeling of male reproductive toxicity studies has several potential flaws." *[Please see docket for details and supporting information]*	ToxStrat (15-19)	5	*Points of departure (PODs), general*
"The Draft Assessment does not present explicit rationales for selecting a particular benchmark dose (BMD) or for choosing BMD over a LOAEL/NOAEL approach. In particular it must be clarified when effects are observed at concentrations above the range of saturable metabolism (i.e., 1-2 ppm for formaldehyde), but extrapolated to doses below the range of saturable metabolism." "In Table 2-10 on pages 2-30 and 2-31, NOAELs are not presented and a discussion of the dose levels used in the studies is not provided, in favor of only presenting the PODa…In the derivation of the cRfC for male reproductive toxicology from Ozen et al. (2002), a POD of 2.91 is listed, with a combined uncertainty factor of 3,000, to yield a cRfC of 0.001 mg/m3. Without knowledge of the assumptions underlying this calculation, the reader cannot evaluate uncertainty and conservatism in the calculation. The lowest concentration tested in the study was 12 mg/m^3, which is 12,000 times above the calculated osRfC. This highlights that there is more uncertainty in the extrapolation than presented.	ACC (0100; 45, 53)	5	*PODs, general; male reproductive toxicity PODs*

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Additionally, the Draft Assessment states (p. xxii): '… higher confidence was placed in the osRfC when the POD was identified close to the range of the observed data.' However, almost all the RfCs and osRfCs were modeled outside of the range of the observed data which introduces substantial uncertainties, none of which appear to be recognized in the draft assessment."			
"Sensory irritation and other annoyance endpoints are inappropriate endpoints for developing RfCs. Sensory irritation of the eyes and upper airways are not considered *adverse* by authoritative bodies and reviews (WHO, 2010; Nielsen et al., 2017; ECHA, 2019a). Perception of, or sensory stimulation by, an irritating substance would not be considered adverse as perceptions of, or stimulations by, an unpleasant smell do not affect the form or function of the tissue or organism. Eye and nasal tract chemosensory detection and nerve stimulation that results from inhalation exposure to formaldehyde is an example of chemesthesis. Chemesthesis is a normal physiological response without functional impairment or pathological change. Thus, sensory recognition of formaldehyde is not adverse and is similar to sensory responses to other chemicals or environmental stimuli such as tearing when exposed to fumes from cut onions or blinking when suddenly exposed to sunlight."	ACC (0103; 63)	5, 3a	*Sensory irritation PODs*
"While the POD for chemosensory detection and adaptive physiological response is not based on an adverse effect, formaldehyde odor detection, resulting in poor air quality, could be considered undesirable for consumers in their homes and workplaces, thus, justifying a guideline value, but not a regulatory limit." "An increase in eye blinking or conjunctival redness is a normal adaptive response to external stimuli and not an adverse health effect. As such, a guideline value may be appropriate for lower concentrations of an irritant chemical (i.e., concentrations below 1 ppm), but developing a RfC based on the potential for adverse health effects on the eyes at lower concentrations is not supported by either individual studies or a weight-of-evidence approach." "Despite the numerous controlled exposure studies that have demonstrated the effective concentrations for preventing eye irritation from formaldehyde, in the Draft US EPA/IRIS Assessment, studies [Hanrahan, Dally et al. 1984; Liu, Huang et al. 1991; Kulle, Sauder et al. 1987; Andersen and Molhave 1983] that are critically flawed and should have been excluded from the determination for dose-response were inappropriately advanced and used to derive or support a RFC of 0.009 mg/m^3 for formaldehyde. In contrast, several controlled human exposure studies that are generally considered to be robust were not used to derive a RFC (Lang, Bruckner et al. 2008, Mueller, Bruckner et al. 2013). It is also well-acknowledged that the ability of a chemical to elicit odor occurs at (significantly) lower concentrations than its ability to elicit sensory irritation (Doty, Cometto-Muñiz et al. 2004). Despite this, the USEPA has proposed a RFC for sensory irritation that is well below the established threshold for odor. This	MCSC (7-8, 9-11, 15)	5, 3a	*Sensory irritation PODs*

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inconsistency arises from the inappropriate use of and support by uninformative epidemiological studies with confounding variables that produce critical flaws. Following are concerns identified among the epidemiological or controlled exposure studies judged with medium confidence [Hanrahan, Dally et al. 1984; Liu, Huang et al. 1991; Kulle, Sauder et al. 1987; Andersen and Molhave 1983] that were used to derive or support a RfC based on sensory (eye) irritation." "Overall, the reliance on historical symptom prevalence reports that are not obtained in conjunction with exposures raises serious concerns that an inappropriately low RFC is being derived. To date, no chemical has been identified as having an irritation threshold that is lower than its odor threshold and formaldehyde is no exception. Reliance solely on the data from the Hanrahan study has resulted in the identification of an irritation threshold that is orders of magnitude below the acknowledged odor threshold. The number of well-conducted controlled exposure trials with no evidence of ocular irritation between 0.3-0.5 ppm provide ample evidence that maintaining exposures at or below these concentrations will provide sufficient protection from sensory irritation, including eye irritation." *[Please see docket for details and supporting information]*			
"We were both co-authors of the Formaldehyde section of the World Health Organization Indoor Air Quality Guidelines for Select Pollutants (WHO 2010). We are concerned that the US Environmental Protection Agency (USEPA) evaluation of noncancer endpoints in the Draft document "Toxicological Review of Formaldehyde—Inhalation" largely ignores several important studies that the formaldehyde working group considered key. These recommendations were further endorsed by peer reviewers, and then the entire set of working groups and their reviewers. The recommendations were also published in a series of peer-reviewed journal papers by two of the WHO formaldehyde working group authors, Drs. Wolkoff and Nielsen...We were disappointed to see USEPA discount use of these high-quality studies [Mueller et al. 2013 and Lang et al. 2008], in favor of a population-based study where exposure was not controlled (Hanrahan et al 1984), which USEPA states was supported by older studies (Kulle et al 1993 or Andersen and Molhave 1983). The rationale provided was that the more recent chamber studies did not find a dose-response relationship. However, we note that one of these studies did not find any effect, even at the highest exposure, and the other study only found mild, chemosensory effects. This seems to discount better conducted studies simply because no effects were observed, which seems to be biased towards finding an effect where none exists. We believe that properly controlled human exposure studies are the "gold standard" for setting safe exposure limits, as they offer the major advantage of having defined exposure conditions, carefully characterizing volunteers, and altering experimental methods to	Ram (0080; 1-3)	5, 3a	*Sensory irritation PODs*

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consider potential confounding factors (Nielsen and Wolkoff, 2017). For example, people can detect the odor of formaldehyde at concentrations as low as 0.1 mg/m^3 (WHO, 2010), which can interfere with subjective reporting of sensory irritation (Cometto-Muñiz and Cain 1991; Brüning et al., 2014). Controlled human exposure studies can add controls that mask these odors and their influence on subjective measures. We hope that USEPA will reconsider the studies serving as the basis of the reference concentration for sensory effects."			
"In addition to these studies [Lang et al. 2008 and Mueller et al. 2013] of irritation following short-term exposures, multiple studies have also been conducted in animals focused on objective measurements of tissue irritation, cell proliferation and cytotoxicity following short-term repeated dose exposures (Swenberg et al. 1983a, 1983b; Monticello et al. 1991; Monteiro-Riviere and Popp 1986). Although some of these studies were discussed by EPA under the category "respiratory pathology" with robust evidence, they are objective evidence of an adverse effect, tissue irritation, following short-term exposures and would thus be more relevant for deriving an irritant RfC." "EPA should use objective measures of adverse effects for developing noncancer RfCs." *[Please see docket for details and supporting information]*	ACC (0103; 64) ACC (0103; 64)	5, 3a	*Sensory irritation PODs*
"On page 1-154 of the Toxicological Review, EPA states that most of the studies reporting histopathological changes in humans had average exposures ranging from 0.05 to 0.6 mg/m3. EPA speculates that these workers are likely less sensitive to formaldehyde than the average person, characterizing them as "survivors" of long-term irritant exposure. This appears to be complete speculation and, to this reviewer, undermines the credibility of the assessment. Notably, there were no high confidence studies in humans. Among the four medium confidence studies, one (Boysen et al. 1990) was characterized by EPA as equivocal. Importantly, all the studies found relatively mild differences in nasal histopathology when plant workers were compared to non-plant workers (see table below). Many of the plant workers were exposed to wood dust and likely other chemicals. As shown in the table below, many of the individuals in the referent groups appear to work in very different professions with different environmental settings (e.g., factory vs hospital). These comparison groups do not appear to be suitable for ascribing any observed differences to formaldehyde with any certainty."	ToxStrat (14)	5, 3e	*Respiratory tract pathology PODs*
"EPA did not derive, and present for comparison, an RfC for upper respiratory tract effects, based on cytotoxicity, as directed by the NAS (2011)." "The Draft Assessment often confuses the difference between an adverse and compensatory response, leading to the development of RfCs based on compensatory rather than adverse responses, which is prohibited by EPA guidelines for risk assessment. Hyperplasia and	ACC (0100; 2, 40)	5, 3e	*Respiratory tract pathology PODs* EPA Note: the draft estimates and discusses

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metaplasia are often compensatory responses, as recognized in the Draft Assessment, but then considered adverse and used for developing RfCs." *[Please see docket for details and supporting information]*			an RfC for cytotoxicity-induced proliferation in the context of cancer.
"The Draft Assessment chose to exclude available data but adds uncertainty factors to the POD to account for lack of these same data. The Draft Assessment (p. 2-28) when justifying an uncertainty factor being applied for extrapolation of subchronic to chronic exposure for respiratory tract pathology states: 'A factor of 3 was applied to the respiratory tract pathology POD from Kerns et al. (1983) because it was based on 18-month exposure data from that rodent study in lieu of the 24-month exposure data available in the same study.' First, it is noteworthy that the 24-month NOAEL for respiratory tract pathology is the same as that defined for the 18-month exposures. Second, the Draft Assessment, in the same paragraph, provides a contradictory analysis by first stating: '…there are data to suggest that exposure concentration would be more important to the development of this lesion than duration' and 'a lower POD would have been expected if the 24- month data could have been modeled.' Speculation on what would be "expected," does not present a strong case for adding uncertainty factors for the absence of the excluded data. Thirdly, there are internal inconsistencies in the Draft Assessment when determining to ignore the 24-month data of Kerns et al. (1983)… There is no rationale for concluding that a preference for a shorter-term value from the same study is inappropriate in one study evaluation, but acceptable for another study evaluation." "The Draft Assessment lacks transparency in the quantitative assessments and conservatism in proposed exposure limits is introduced by the use of modeling practices and exposure concentration adjustments that are ill defined. In addition, insufficient rationale is provided and most often relegated to footnotes. Some resulting uncertainty adjustments exceed the limits defined by EPA."	ACC (0100; 44)	5	*Uncertainty factors (UFs); Respiratory Tract Pathology PODs*
"…EPA should focus on the area of critical effect and not belabor effects that are clearly well advanced in formaldehyde's underlying mode of action. For example, estimating a Reference Concentration (RfC) for a pathological endpoint that only occurs well above a No Observed Adverse Effect Level (NOAEL) for tissue irritation is non-sensical. Furthermore, EPA has some exquisite human data in hand including data in sensitive subgroups. EPA needs to recognize that a NOAEL for such data are, in effect, the RfC, as per its own definition of RfC. In such cases, no additional uncertainty factors are needed for within-human variability, as readily demonstrated by prior EPA judgments found on its Integrated Risk Information System (IRIS)."	TERA (0078a; 1-2)	5	*Organ- or system-specific RfCs (osRfCs); UFs*

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"The Draft Assessment presents RfCs for a number of non-cancer systemic effects, including reproduction/developmental effects in females and reproductive toxicity in males. NAS (2011) identified this as problematic and not supported by the evidence." "The Draft Assessment does not integrate available data, as required when reaching conclusions; individual RfC and Inhalation Unit Risk (IUR) factors were calculated based on individual study results with only uncertainty factors added and/or linear extrapolations. The exception is an inappropriately averaged RfC for female reproductive or developmental toxicity." *[Please see docket for details and supporting information]*	ACC (0100; 5; 26, 57)	5	*osRfCs; Responsiveness to NAS (2011)*
Charge Question 6: Cancer Hazard Identification			
"The classification of 'evidence demonstrates' that formaldehyde causes nasopharyngeal cancer (NPC) and sinonasal cancers is not fully supported and should be reevaluated based on the growing amount of information which argues against a causal association. Based on EPA guidelines (Table 8 of EPA 2022a), the classifications of 'evidence indicates' is more appropriate given the conflicting and inconsistent findings in human epidemiological studies, the indications of chance, bias and confounders in key positive epidemiological studies, and the stronger but limited evidence in high exposure rat studies."	LCA (2)	6a	*Upper respiratory tract cancers*
"European Union regulations for formaldehyde Formaldehyde is a very well-known chemical. It is one of the first that having registered under the EU REACH regulation (EC) No 1907/2006 and benefits from decades of extensive scientific research. Formaldehyde is already highly regulated: consumer and worker safety are ensured in the European Union via harmonised classifications under the (EC) No 1272/2008 Regulation, existing and forthcoming REACH restrictions and the implementation of an EU-wide Binding Occupational Exposure Limit (BOEL). This BOEL is based on the evaluation of the European Scientific Committee on Occupational Exposure Levels (SCOEL) which derived an occupational exposure limit (OEL) of 0.3 ppm TWA and a short-term exposure limit (STEL) of 0.6 ppm. The opinion of the SCOEL was joint to this submission. An important prerequisite for the derivation of these exposure limits was the categorization as a so-called group C carcinogen, i.e. a genotoxic carcinogen with a mode-of-action based threshold. For all relevant steps of local carcinogenesis, clear No-Observed-Adverse-Effect-Concentrations (NOAECs) could be identified (cf. page 9 of the [submitted] joint SCOEL document): 'Experimental studies support that the local carcinogenesis at the portal-of-entry is pivotal. In the sensitive rat species, the apparent LOAEC was 6 ppm, and the apparent NOAEC was 2 ppm	Form (0085a; 1-2)	6	*Upper respiratory tract cancers; Cancer MOA* EPA Note: Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.

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for nasal cancer. Experimentally, the histopathological NOAEC for nasal effects of FA in rats and monkeys is 1 ppm and the NOAEC for regenerative cell replication is 2 ppm. At these NOAECs, the FA-DNA adducts were less in monkeys than in rats as was the relationship of exogenous/endogenous DNA adducts, which is in line with the assumption that humans should be a less sensitive species. The new studies confirm that local FA-DNA adducts show a highly non-linear relationship with external FA exposures. At ≤ 2 ppm FA, the FA DNA-adducts induced by external exposures comprise a minor portion of the total FA-DNA adducts, which were driven mainly by internal (naturally generated) FA. This is supported by considerations on toxicokinetics, concluding that the intracellular FA concentration increases only slightly, and the intracellular glutathione concentration decreases only slightly in this range and that the homeostasis within the epithelial cells would not be affected. Therefore, the apparent NOAEC of 1 ppm can be considered a mode-of-action based NOAEC for carcinogenic effects at the portal-of-entry.'"			
"EPA failed to consider Thompson et al. (2020), which provides important data integration related to the MOA for formaldehyde-induced nasal tumors." "The Draft Assessment does not follow the EPA Framework in presenting alternative MOAs and including the empirical support for each. This is directly relevant to the discussion of the cytotoxicity and regenerative hyperplasia MOA for nasal tumors related to inhaled formaldehyde. The Draft Assessment does not reference the Thompson et al. (2020) IPCS MOA analysis for formaldehyde-related nasal tumors that updated the McGregor et al. (2006) assessment. This despite written and oral communications to the EPA from the authors and sponsors. Rather the Draft Assessment acknowledges the MOA as defined by McGregor et al. (2006), as updated by Thompson et al., but without referencing those peer-reviewed publications (see quote below). Furthermore, the Draft Assessment dismisses the MOA, in favor of a mutagenic MOA, without making a quantitative assessment of the cytotoxicity with regenerative hyperplasia MOA as directed by the NAS (2011)." "the Draft Assessment does not include a fair evaluation of the most widely accepted MOA for nasal tumor formation related to formaldehyde and does not follow EPA Cancer Guidelines [See also general comments on lack of documentation for MOA]... The exclusion of Thompson et al. (2020) from the Draft Assessment is noteworthy, as Dr. Thompson personally briefed the EPA IRIS staff on the peer-reviewed and published cytotoxicity MOA. This MOA for nasal tumors was recently adopted by the European Chemicals Agency (ECHA) and approved by the 32 countries in the European Union." *[Please see docket for details and supporting information]*	ACC (0103; 56)	6	*Upper respiratory tract cancers; Cancer MOA* EPA Note: Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.

Comment	Commenter (PDF #; page)	Charge Question(s)	EPA Notes and *Topic Characterization*
"The EPA IRIS Draft recognized the potentially important rold of epigenetic regulation in MOA of nasal tumor, yet further data from animal and human studies are needed...I appreciate that the EPA IRIS Draft recognized the potential important role of epigenetic regulation in the MOA of formaldehyde by stating 'DNA methylation and histone modification can promote carcinogenesis through steric regulation of enhancer/promoter binding and transcription factor-DNA association, thereby affecting gene transcription' and 'suggesting that these epigenetic effects may play a causal role in human URT cancer formation.' However, no studies have exclusively examined histone PTM and DNA methylation in formaldehyde-exposed animals or human. Therefore, the data used in the IRIS Draft were largely limited to cultured cells or results based on N6-Formyllysine that is not a highly relevant biomarker of formaldehyde exposure and epigenetic regulation, which represents a significant data gap in understanding MOA of formaldehyde-induced nasal tumor." "Recommendation: Further studies (animal and human) are needed to improve understanding of the role of mutation and epigenetic factors, including histone modification and DNA methylation, contributing to the cytotoxicity with regenerative hyperplasia MOA." *[Please see docket for details and supporting information]*	UNC (37-40)		*Upper respiratory tract cancers*
"The following review articles relevant to the MOA of formaldehyde and thus the U.S. EPA risk assessment are not cited anywhere in the Toxicological Review, Assessment Overview, or Supplemental Information. It is unclear if these articles were not captured in U.S. EPA's literature searches or whether they were captured but intentionally discarded by the U.S. EPA [Thompson et al. 2020; Gentry et al. 2020; Andersen et al. 2019; Thompson et al. 2018]. "U.S. EPA failed to integrate two highly relevant data streams [studies in ADH5 null mice and measurement of endogenous and exogenous formaldehyde-DNA adducts] into their MOA analysis." "Individually, the studies described above may not paint a coherent MOA for formaldehyde. In totality, however, they tell a remarkably cohesive picture of the likely MOA for formaldehyde-induce nasal tumors. Instead of integrating these data, the U.S. EPA documents are full of speculative discussions of what might theoretically be capable of happening as evidenced by their refusal to develop either a linear or non-linear MOA and instead display networks of plausible mechanistic effects. If there is a study or studies that report that formaldehyde causes, for example, inflammation in the portal of entry and/or systemic tissues, then EPA accepts these effects at face value and further hypothesizes that they could play a meaningful role in an otherwise overly complex intractable MOA while ignoring high-quality molecular data that tell a remarkably coherent study. This is not how risk assessment should be conducted."	ToxStrat (3, 6, 8-13)	6	*Upper respiratory tract cancers* EPA Note: Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.

Comment	Commenter (PDF #; page)	Charge Question(s)	EPA Notes and *Topic Characterization*
"Assuming the term "in silico" on page 1-302 was an error and that U.S. EPA instead meant "in vivo" test systems have shown formaldehyde to induce genotoxic or mutagenic effects, this statement too is misleading. As discussed in Thompson et al. (2020), genotoxicity assays conducted in the nasal tissues of rats have reported negative findings for clastogenic and mutagenic markers. As already discussed, ADH5 null mice do not exhibit increases in markers of genotoxicity unless other genes involved in formaldehyde detoxification of DNA repair are also knocked out." "The nasal tumor MOA information provided in the Toxicological Overview is neither clear nor well-constructed. Section 4.2.3. Mode of action information, of the Toxicological Overview is vague and provides no graphical depiction of the hypothesized MOA. Table 34 lists "hypothesized mechanistic events" with no clear indication of the sequence of events. The first mechanistic event is "direct, or presumed direct, genotoxicity and mutagenicity". The reviewer assumes that U.S. EPA has chosen the word 'presumed direct' because much of the evidence for this key event in animals is based on markers of exposure (e.g., DNA adducts and DNA-protein crosslinks) as opposed to markers of effect (e.g., evidence of clastogenic or mutagenic damage)." "It is curious that the only real evidence for "direct" genotoxicity and mutagenicity comes from worker and student studies. The use of the term "direct" is highly misleading, as these are not controlled experiments and the workers and students were likely exposed to other agents (chemical or physical) that might increase micronuclei. Notable omissions from Table 35 are Speit et al. (2007) and Zeller et al. (2011)." "Table A-22 "Summary of in vivo genotoxicity studies of formaldehyde inhalation exposure in experimental animals" is highly misleading regarding the evidence for in vivo genotoxicity in regions where tumors occur. A total of five studies is listed in the table section "Mutations." Two of the 5 studies are based on the same underlying bioassay where rats were exposed for 2 years (Recio et al. 1992, Wolf et al. 1995). These studies looked for p53 mutations in tumor tissue, which is not a valid approach for assessing whether genotoxicity is an early initiating event in the MOA. Another study, Kitaeva et al. (1990) is in Russian and appears to have reported genotoxicity in bone marrow cells even though the highest exposure concentration was 1.5 mg/m3, which is not even carcinogenic to the nasal passages of rodents. The fourth positive study is Liu et al. (2009), where male mice were exposed to 0, 2, 20, or 200 mg/m^3 formaldehyde for 2 hours and then mated six weeks later. Exposure to 200 mg/m^3 was reported to increase heritable mutations in offspring. It should be appreciated that the RD50 for mice is ~5 mg/m3 (see Table A-16 in the Supplemental Information). It is conceivable that exposure to 200 mg/m^3 would have depressed respiration much further. Data presented in			

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section A.3 discusses that this reflex bradypnea induces hypothermia in mice (decreasing body temperature by as much as 14 degrees). In addition, U.S. EPA states that reflex bradypnea "also results in decreased blood pO2 and pCO2 and increased blood pH." It is well known that hypothermia can cause genotoxicity (Tweats et al. 2007). This has no relevance to humans because exposure to irritant gases does not result in extreme levels of heat loss due to the much lower surface area to volume ratio of large mammals compared to small mammals (Gordon et al. 2008). The fifth study in this section, Meng et al. (2010) did not find increases in mutant frequency in nasal tissue following exposure up to 18.5 mg/m^3 for 13 weeks. This is the only relevant study in this section of the table." "Table A-22 section "Micronucleus" lists only one study reporting on micronuclei in tissue other than blood or bone marrow. Specifically, Neuss et al. (2010) is listed as negative for micronucleus formation in bronchioalveolar lavage cells. Missing from the table is Speit et al. (2011), which reported no increases in micronucleus formation in rat nasal tissue following 4 weeks of exposure up to ~18 mg/m^3 formaldehyde. It is unclear why this study was not included in the table. The vast majority of studies listed in Table A-22 includes either genotoxicity effects beyond the portal of entry or DNA modifications in the nasal and other tissues. These modifications are not measures of heritable gene changes, and thus should not be considered genotoxicity. As already discussed, data in ADH5 null mice indicate that increased formaldehyde DNA adducts are not necessarily genotoxic." "In discussing the role of cell proliferation, U.S. EPA cites evidence for increased cell proliferation ≤2.5 mg/m^3 as evidence for mitogenic proliferation that might increase cancer risk together with DNA damage. As already noted, these levels can result in squamous metaplasia, i.e., a transition from respiratory to squamous epithelium. As such, comparing the labelling index between treated and control animals is essentially comparing the proliferation rate in two different epithelial types." "On page 1-331, U.S. EPA states that glutaraldehyde cause many of the same effects as formaldehyde (squamous metaplasia, hyperplasia, and inflammation) yet does not increase nasal tumors. U.S. EPA uses this to conclude that increased cell proliferation alone is not sufficient to cause nasal tumors...To my knowledge, the MOA of glutaraldehyde has not been studied as extensively (if at all) as formaldehyde since 2006. As such, the database for glutaraldehyde is insufficient to inform the MOA of formaldehyde." "Table 35 lists 'cellular mitogenesis in the absence of cytotoxic tissue pathology' as another hypothesized mechanistic event. In the column titled 'experimental evidence pertinent to mechanistic event' there is a bullet stating that there is clear evidence for increased URT 'cell proliferation under conditions also resulting in tissue pathology' at ≥4 mg/m^3. Unless this bullet			

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includes a typo, it is unclear how that bullet supports the hypothesized event. The next bullet states that there is 'suggestive evidence' for increased URT 'cell proliferation under conditions not clearly causing tissue pathology' <4 mg/m^3. This bullet does support the hypothesized key event; however, note the overall weak terminology such as 'suggestive evidence' of cell proliferation 'not clearly causing' pathology. This language is weak and its purpose seems to be to establish cell proliferation at exposure concentrations more relevant to human exposure levels than the higher concentrations clearly associated with increasing cell proliferation and tumors in rodents." "The U.S. EPA should revise its assessment such that the presence of DNA-protein crosslinks and formaldehyde-DNA adducts is not synonymous with genotoxicity." "Much of the text on pages 1-315 to 1-320 includes discussion about the accumulation of DNA-protein crosslinks. This accumulation is discussed in the context of Leng et al. (2019) who reported that exposure to ≤0.3 ppm formaldehyde for 28 days did not result in the detection of exogenous formaldehyde-DNA adducts. U.S. EPA appears to be speculating that longer exposure durations to low concentrations might increase adducts. If accumulation were true, then one might expect that the constant biological production of endogenous formaldehyde would increase the levels of endogenous adducts over time. I am not aware of any articles that have demonstrated this. Considering that U.S EPA believes formaldehyde adducts are pro-mutagenic but also acknowledge that nasal tumors in rodents are exceedingly rare, it would seem that endogenous adducts do not accumulate over time and nor would any exogenous adducts formed from exposure to ≤0.3 ppm formaldehyde accumulate over time. The U.S. EPA also fails to consider that evidence for accumulation of exogenous adducts over time might be due, in part, to remodeling to squamous epithelium where the superficial cell layers are dead yet likely accumulate exogenous adducts as exposure duration increases." *[Please see docket for details and supporting information]*			
"The 2005 Guidelines provide that while a linear extrapolation would generally be the default for DNA reactive chemicals, a threshold approach would be allowed given sufficient evidence. The descriptor "Not likely to be carcinogenic to humans at concentrations that do not cause nasal tumors in rodents" should be used, as should a threshold approach for deriving a toxicity value." "Animal evidence clearly demonstrate a threshold for induction of squamous cell carcinoma, which corresponds to concentrations above where cell proliferation is induced (Monticello et al. 1991; Connolly et al. 2002 as cited in BfR 2006; Swenberg et al. 1980; Kerns et al. 1983; Monticello et al. 1996)."	ACC (0083b; 5) ACC (0103; 8, 54-56)	6a, 6b, 6f, 7a	*Upper respiratory tract cancers*

Comment	Commenter (PDF #; page)	Charge Question(s)	EPA Notes and *Topic Characterization*
"EPA grossly misinterpreted the work of Dr. Marsh, which the 2022 Draft Assessment cites throughout…Of the Marsh et al. papers that were not cited in the 2022 Draft Assessment, EPA omitted the following important studies… [Marsh et al. 2019, Marsh et al. 2014, Marsh and Youk 2004]…The 2022 Draft Assessment also misinterprets and misrepresents several of the Marsh et al. papers that it cites. [Marsh et al. 1996, Marsh et al. 2007b, Marsh and Youk 2005, Marsh et al. 2007, Mart et al. 2016, Marsh et al. 2002]." "EPA's Cancer Guidelines emphasize 'a critical analysis of all the available information that is relevant to assessing the carcinogenic risk,' rather than reliance on default options as the starting point.[16] A nonlinear approach should be utilized when, as in the case of formaldehyde, 'there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses.' The Cancer Guidelines also stress the importance of relying upon, 'common sense reasonable applications of assumptions and policy, and transparency…to avoid unrealistically high [risk] estimates.' *[Please see docket for details and supporting information]*			
"Page 159, lines 3-11: Comment 1: Marsh et al. (1996) concluded that the NCI cohort formaldehyde exposure estimates may be inflated in Plant 1 plant of the NCI cohort study (Plant 1 in Wallingford, CT), where many of the NPC cases occurred, all of which were associated with the highest exposure categories. The 2022 draft interpretation suggests that all exposures in the NCI study, which includes 10 plants, would have been impacted by exposures in Plant 1, and thus that the true risk would have been overpredicted in the entire study. This is a serious misrepresentation of the Marsh et al. (1996) findings that were limited to Plant 1." "Page 1-209, lines 1-11: Comment 2: This is the source of the serious misrepresentation noted in Comment 1 above which could potentially mislead the reader to believe that all risks were understated in the NCI cohort study." "Page 1-209, lines 32-39, Page 210, lines 1-3: Comment 3: The 2022 IRIS draft fails to consider Table 6 in Marsh et al 2007b, which reported results based on the interaction terms used in the case-control study modeling. This showed that when comparing workers with formaldehyde exposure only to workers with neither formaldehyde nor silversmithing or other metal work exposure there was no elevation in the risk of NPC. In contrast, when comparing workers with silversmithing or other metal work to workers with only formaldehyde exposure the odds ratio for NPC was 13.37. These findings suggest that co-exposures to silversmithing or other metal work, which include risk factors for NPC and other upper respiratory system cancers, played a major role on the NPC findings that were unique to Plant 1 in the NCI study. These findings were essentially disregarded by the 2022 IRIS draft.	Cardno (0082; 2-5)	6a	*Upper respiratory tract cancers*

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Marsh et al. (2007b) also reported but did not show results of interaction models for the category all other pharyngeal cancers (AOPC) that generally produced more robust risk estimates due to the larger number of cases. For example, the conventional baseline model further adjusted for year of hire revealed a 4.32-fold increased risk for subjects with silversmithing or other metal work only, whereas subjects exposed only to formaldehyde had no elevated risk of AOPC. Here subjects with both exposure factors had a decreased risk for AOPC due to the heavy influence of subjects with formaldehyde exposure only (10 of 16 cases)." "Pages 1-210; lines 3-16: Comment 4: EPA's argument that the results for NPC in the NCI cohort consistently show an association between formaldehyde and NPC risk is not supported by the data in Table 2 of the Marsh and Youk (2005) paper. Specifically, Table 2 shows that the SMR based on local rates for NPC among Plant 1 workers was 7.39 and statistically significant based on 6 of the 10 total NPC deaths in the NCI cohort study. In stark contrast, the corresponding SMR for workers in the remaining nine plants in the NCI study was 0.98 -- essentially a null value. This finding highlights the inconsistency of the results in the NCI cohort study and shows clearly that Plant 1 was unique with respect to non-formaldehyde risk factors for NPC. In the Marsh et al. (2007) case-control study discussed in Comment 3, it was concluded that the unique and profound findings for NPC in Plant 1 were likely due to risk factors associated with exposures in previous or post-Plant 1 jobs in the silversmithing or other metalworking industry. The authors stated "the results of our nested case-control study suggest that the large NPC mortality excess in the Wallingford cohort (Plant 1) may not be due to formaldehyde exposure but rather reflects the influence of external employment in the ferrous and nonferrous metal industries of the local area that entailed possible exposures to several suspected risk factors for upper respiratory system cancer (e.g., sulfuric acid mists, mineral acid, metal dusts and heat)". This association reported in the Marsh et al. (2007) publication was given no consideration in the 2022 IRIS draft." "Page 1-210, lines 34-37: Comment 5: While no specific Marsh citations were stated in this conclusion, it should be noted that this conclusion is not consistent with that reached by Marsh and colleagues in several papers, most recently Marsh et al. (2016). In this second reanalysis of the NCI cohort data Marsh et al. concluded "Our updated analysis provided little or no evidence to support NCI's suggestion of a persistent association between formaldehyde exposure and mortality from NPC. NCI's suggestion continues to be driven heavily by anomalous findings in one study plant (Plant 1)." This and earlier Marsh et al. reanalyses of the NCI formaldehyde cohort demonstrated that the results of the NCI study for NPC mortality were driven heavily by the results in Plant 1 which ultimately included six of 11 NPC cases. As noted in the above			

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comments, Marsh et al. (2007) found that the NPC excess unique to Plant 1 was likely due to external exposures in the ferrous and nonferrous metal industries of the local area." "Page 1-239, Table 1-33: Comment 6: The Marsh et al. (2007a) citation is incorrectly stated in the reference list. This actually should be what is stated as 2007b." "Page 1-254, Lines 1-8: Comment 7: The 2022 IRIS draft cites only SMRs based on US rates, whereas the Marsh et al. (2007b) article also provided the more valid SMRs based on local county population rates. In this case, the local rate based SMRs were lower than those cited by IRIS." "Page 1-254, lines 15-19: Comment 8: This is a confusing and incorrect statement because the Marsh et al. (2002) paper did not present results for oropharyngeal / hypopharyngeal cancer in relation to years of formaldehyde exposure. Results were presented for the category "all pharyngeal cancer" and the category "NPC only." It appears that EPA re-calculated SMRs using data from the Marsh et al. (2002) paper. As noted below, there may be errors in EPA's calculations of the confidence intervals." "Page 1-254, lines 29-34: Comment 9: Same response as comment 8." "Page 1-255, lines 3-5: Comment 10: First, this reference should be Marsh et al (2007b). Second, the results shown for hypopharyngeal and pharyngeal cancer unspecified are reversed. Third, no mention is made of the local rate-based SMRs for these categories, which in every case were lower than those based on US rates." "Page 1-255; lines 3-5: Comment 11: The SMRs and CIs for Marsh et al. (2002) 'Exposure to formaldehyde >0.2ppm' were "calculated using the Mid-P method" by EPA, but could not be replicated in calculations using the specifications in the table footnotes; specifically, the CIs calculated were different than I calculated using the stated methods. Per my calculations, the Level 1 SMR and 95% CI should be 1.51 (0.61-3.13) and the Level 2 SMR and 95% CI should be 2.01 (0.98-3.68). As a result, the Level 2 95% CI would no longer be considered statistically significant as our calculated lower bound is less than one. These errors in calculations thus could have affected how EPA interpreted Marsh et al. (2007b); these calculations should be corrected and the updated conclusions incorporated accordingly."			
"For the evaluation of MOA information, EPA notes that 'in general, studies relevant to mechanistic interpretations informing hazard identification were not individually evaluated.' However, the sections that follow indicate that some data were assessed for risk of bias and other domains, but with differing methods for each endpoint. For non-cancer respiratory mechanistic studies, EPA follows the general Handbook framework for rating these studies as low, medium, or high confidence. For mechanistic studies of non-cancer extra-respiratory effects, such as circulating blood cells, however, it appears no confidence evaluations were	ACC (0083a; 4-5, 7) ACC (0100; 69, 70) ACC (0103; 12-14, 57)	6, 3	*Cancer MOA; Noncancer MOA*

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conducted, despite the fact that some of these studies have been used to inform carcinogenic hazard in the LHP malignancies (see page A-554)." "Finally, for epidemiological studies of genotoxic endpoints, a third process was used, which is summarized as follows: '...an overall conclusion of "no obvious bias" was used if no concerns were identified. for studies with a potential bias identified, the potential bias or issue was summarized in the comment row. For each assay (e.g., chromosomal aberrations, CBMN, Comet assay), factors related to assay methods that could affect the endpoint values were identified using published reviews from collaborations that compared assay methods across epidemiological studies (Fenech, 2020; Moller et al., 2020; Bonassi et al., 2011; Fenech et al., 2011; Valverde and Rojas, 2009; Bonassi et al., 2005).' Interestingly, on page A-222, the mechanistic epidemiological study by Zhang et al., (2010), which has been all but refuted in a number of peer-reviewed publications (see, for example, Gentry et al., 2013; Mundt et al., 2017) is discussed only briefly by EPA; the comment column simply states, 'small sample numbers, no obvious bias.' The Gentry and Mundt papers are also cited, but the re-analyses presented in these studies are largely dismissed and not integrated with Zhang et al. (2010) or any of the other human studies evaluating markers of genotoxicity." "The Draft Assessment relies on multiple assumptions [regarding MOA] rather than considering alternative viewpoints supported by data in the formaldehyde literature." "Discussion of MOA is more often speculative than grounded in empirical demonstration." "EPA misinterprets Recio et al. (1992) to support an implausible genotoxic mode-of-action for carcinogenicity." "EPA provides no criteria for its process for considering the strength of the mechanistic studies for genotoxic findings. EPA should standardize its approach to considering mechanistic and MOA studies and apply it consistently across endpoints. Mechanistic and MOA data should not be relegated to 'supplemental information' but more fully integrated into the assessment beginning early in the IRIS process." "The 2022 Draft Assessment does not incorporate best practice recommendations from NASEM and other agencies on the evaluation and integration of MOA information...Other systematic review frameworks recommend evaluating mechanistic information and information on potential MOAs with the same level of rigor as the other lines of evidence (animal and human). WHO (2021) is particularly clear on this matter, stating: 'Regarding mechanistic and pharmacokinetic data (two separate types of data), these are often described as being contextual or associated with sub-questions. However, if these data are anticipated to be critical in making determinations of hazard or dose– response, such data should be included in the review and subjected to the same appraisal and structured evaluation process applied for			

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other data types (emphasis added).'…The 2022 Draft Assessment, however, does not appear to implement any of these best practices for the use of mechanistic studies and MOA information. Mechanistic studies and information supporting (or not supporting) MOA are largely relegated to "supplemental" information and considered only in the evidence integration phase in the context of their ability to inform hazard conclusions based on human and animal evidence." "The 2022 Draft Assessment does include more discussion of MOAs relative to the 2010 Draft Assessment. EPA acknowledges that inhaled formaldehyde is not distributed to an appreciable extent beyond the respiratory tract to distant sites. EPA, therefore, assumes inhaled formaldehyde acts via a different pathway. Although EPA looks at endpoints that could be key events in an MOA, EPA has not proposed a biologically plausible MOA…In fact, the postulated MOA is lacking any experimental data to support EPA's conclusion that inhaled formaldehyde that EPA acknowledges is not distributed to sites beyond the portal of entry and causes cancer." "The 2022 Draft Assessment's treatment of MOA and mechanistic data renders it inappropriate for regulatory use…EPA's dismissal of the importance of MOA and mechanistic information is inconsistent with the Agency's own approach to human health hazard assessment for a given chemical under the Toxic Substances Control Act (TSCA), one of the stated objectives for the 2022 Draft Assessment. EPA's guidelines governing application of systematic review in TSCA risk evaluations characterizes the 'the availability of a fully elucidated mode of action (MOA) or adverse outcome pathway (AOP)' as 'highly preferred.' These guidelines argue that '[m]echanistic evidence may provide support for biological plausibility and help explain differences in tissue sensitivity, species, gender, life-stage or other factors,' emphasizing that 'EPA/OPPT plans to prioritize the evaluation of mechanistic evidence instead of evaluating all of the identified evidence upfront. This approach has the advantage of conducting a focused review of those mechanistic studies that are most relevant to the hazards under evaluation.'" *[Please see docket for details and supporting information]*			
"I believe there is an issue with the interpretation of a manuscript that I was the senior author… the p53 point mutations observed in the Recio et al. (1992) study, which EPA cites as evidence of a formaldehyde-induced initiating event in their draft document, is not plausible for several reasons…There is no pathway for DPC to cause the point mutations observed exclusively at GC base pairs. Genotoxicity observed in respiratory tissues are not measures of mutagenic events, particularly point mutations: genotoxicity [does not equal] mutagen[i]city. There is no evidence to support a temporal nature of a mutagenic carcinogen as outlined by EPA. Finally, as determined by NTP, there is no data to support a role for p53 in formaldehyde-induced neoplasia. Although I recognize that p53 mutations are considered hallmarks of cancer,	SV (1-2)	6e, 6f	*Cancer MOA*

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the concern I have is the misrepresentation in your review of the Recio et al., 1992 manuscript indicating that these late occurring mutations are caused by formaldehyde induced DNA lesions. With the lack of any data to support a mutagenic event prior to tumor outcome in the target tissues, I conclude that the p53 mutations observed in SCC from formaldehyde exposed rats are late occurring passenger mutations resulting from known genome instability that occurs in cancers, are not formaldehyde-induced point mutations and do not support a mutagenic mode-of-action for tumor outcomes from formaldehyde exposed rats."			
"...the SBA cautioned EPA against 'making definitive conclusions about causes based on evidence that only demonstrates association and without identifying a mode of action' while identifying nearly a dozen key studies excluded by EPA and repeatedly warning that EPA 'does not have a mode of action or mechanistic evidence' supporting its core conclusions.[10]" "Additional interagency concerns were identified during internal review, such as the Agency for Toxic Substances and Disease Registry (ATSDR) statement that the lack of mechanistic data 'needs to be a reason to down-grade the evidence findings. It is significant.'"	USCC (4)	6, 3	*Cancer MOA; Noncancer MOA* EPA Note: Interagency reviewer (e.g., ATSDR; SBA) comments were on a draft prior to revision for public release. Please consult the full interagency review comments in the EPA docket.
"The IRIS Draft did not recognize the importance of development of chemical-specific biomarker of formaldehyde exposure/molecular dosimetry data in its evidence-based risk assessment...Due to the absence of data for formaldehyde-specific biomarkers, the EPA IRIS Draft could not unambiguously assess the differential contribution of formaldehyde when cofounding factors, such as methanol co-exposure, when present...How could the IRIS draft conduct rigorous evidence-based risk formaldehyde assessment using only data based on non-formaldehyde specific approaches that do not involve formaldehyde-specific biomarkers and could not provide accurately measure the contribution of exogenous formaldehyde under the substantial endogenous background of formaldehyde?" "Recommendations: The EPA IRIS Draft needs to discuss the limitations of available data/methodologies, highlight the significance of SILMS-generated formaldehyde-specific biomarker data, and integrate dosimetry data provided by the rich formaldehyde-specific biomarker data into risk estimates of formaldehyde." "The IRIS Draft misunderstood or underestimated the significance and utility of stable isotope labeling and mass spectrometry methods in understanding the potential for formaldehyde carcinogenicity and its use in characterizing dose-response in quantitative risk assessment...The ability to distinguish DNA damage caused by exogenous formaldehyde from substantial	UNC (2-9, 34-37)	6, 2, 7	*Cancer MOA; Endogenous formaldehyde; cancer dose-response*

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background endogenous formaldehyde-induced lesions is crucial. Accurate molecular dosimetry of both endogenous and inhaled formaldehyde is essential for science-based risk assessment of formaldehyde exposure." "Recommendation: The EPA IRIS Draft needs to discuss the utilities and advantage of SILMS and, thus, to use the rich datasets we generated over the last decade to improve evidence-based risk assessment of formaldehyde." "The IRIS Draft did not appreciate and interpret key data on the kinetics studies of formaldehyde-induced DNA adducts... The EPA IRIS Draft noticed the results of the time-course exposure study by stating 'rat nasal N2-hmdG adduct formation was also positively associated with exposure duration, with adducts accumulating to levels >/=5 times higher after 28 days of exposure to 2.5 mg/m^3 compared to single exposures.' However, the IRIS Draft did not provide any discussion on the repair/loss and half-life of formaldehyde-induced DNA adducts, which is quite surprising as information on the fate and repair/loss kinetics is essential to assess mutagenicity and carcinogenicity of a genotoxicant like formaldehyde." "Recommendation: The IRIS Draft needs to be revised to discuss the kinetics data on formaldehyde-induced DNA adducts, half-life and the steady state of exogenous DNA adducts to more accurately characterize mutagenicity and genotoxicity of formaldehyde in an evidence-based risk assessment." *[Please see docket for details and supporting information]*			
"The adoption of the KCC approach by the U.S. EPA indicates that risk assessment is, depending on one's point of view, (d)evolving into an anti-hypothesis, anti-expert, anti-MOA approach of simply demonstrating that a chemical has certain characteristics in common with other carcinogens as opposed to understanding how a chemical causes a specific tumor. It is noteworthy that lead author on the KCC approach (Smith et al. 2016; Smith et al. 2020) is also a coauthor on epidemiological studies linking inhaled formaldehyde exposure to leukemia (Zhang et al. 2010; Zhang et al. 2009). Instead of using the KCC approach, the U.S. EPA should follow its own guidance for the risk assessment of carcinogens as described in U.S. EPA (2005)." "Page 1-302 states that formaldehyde has been shown to be genotoxic or mutagenic in a variety on in silico and in vitro test systems. To what is EPA referring regarding in silico test systems? A search of the Toxicological Review for the term "silico" revealed no additional hits. A search of the Supplemental Information for the term "silico" revealed one hit in a citation for Yoo & Ito (2018a). Searching for "Yoo" revealed the study in Table F-12 "Mechanistic studies relating to respiratory tract cancers, focusing on genotoxicity additional hits" where the study was listed as "not impactful." As was discussed in Thompson et al. (2020), BBDR in silico modeling suggests that formaldehyde-induced nasal tumors in rats could be predicted with little or no direct mutagenic contribution from DNA-protein crosslinks as the nasal tumors could	ToxStrat (1-2, 7, 11)	6, 7	*Cancer MOA; Responsiveness to NAS (2011)*

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be explained by mutations accumulating from increased regenerative cell proliferation (Conolly et al. 2003)." "Pertinent to the release of the US EPA's External Review Draft of Toxicological Review of Formaldehyde-Inhalation I was surprised to see that a 2020 review article I coauthored on the mode of action of formaldehyde-induced nasal tumors in Critical Reviews in Toxicology[1] was not cited anywhere in the 193-page Assessment Overview, 789-page Toxicological Review, or the 1058-page Supplemental Information documents[2]. This omission by the U.S. EPA is unfortunate as there are critical data integration topics in the review article that might have informed U.S. EPA's assessment. Moreover, Thompson et al. (2020) is an update of the mode of action (MOA) for formaldehyde-induced nasal tumors published by McGregor et al. (2006), which the U.S. EPA did cite in their assessment. As such, the omission of Thompson et al. (2020) is disappointing." "Below are comments relevant to the missing Thompson et al. (2020) article (and others), additional comments relevant to the MOA evaluation for formaldehyde-induced nasal tumors, as well as separate comments related to some of the noncancer evaluation in the U.S. EPA (2022) assessment. Broadly speaking, these comments highlight the following: • Failure to integrate relevant science into the MOA for nasal tumors in rodents • Failure to response appropriately to previous review by the National Research Council • Failure to adhere to U.S. EPA MOA guidance and practices • Failure to consider nonlinear approaches for protecting against upper respiratory tract cancers • Failure to use appropriate benchmark dose modeling software and practices • Poor organization of the various assessment documents" *[Please see docket for details and supporting information]*			
"NRDC supports the EPA conclusion that – with its highest rating of confidence - "evidence demonstrates" a causal link between formaldehyde exposure and three cancer endpoints, nasopharyngeal cancer (NPC), myeloid leukemia and sinonasal cancer (SNC). NRDC agrees that this is consistent with the scientific evidence." "The 2010 IRIS report that "the associations between myeloid leukemia and formaldehyde exposure are positive and consistent" and that "human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer ... [and] myeloid leukemia." There are no post-2010 data that casts doubt upon that connection. The risk of this endpoint should be included in EPA's overall cancer risk."	NRDC (2-3, 5-6)	6	*Myeloid leukemia; Upper respiratory tract cancers*

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"NRDC supports EPA's evaluation that the scientific evidence demonstrates that exposure to formaldehyde causes myeloid leukemia. Although EPA has "low" confidence in its risk estimate for myeloid leukemia (compared to "medium" confidence in its NPC-based risk figure) EPA could increase scientific confidence in the data by leveraging the meta-analysis of Zhang et al 2009 (discussed above) to support the risk estimate. Use of the meta-analysis can increase the precision of an effect estimate, by basing the estimate on a larger number of studies ,and can also be used to quantify effects across sufficiently homogeneous studies. Meta-analyses frequently underpin Health Impact Assessments (HIA) and cost-benefit analyses (CBA) of interventions, such as policies to reduce air pollution. Meta-analyses can provide important opportunities when synthesizing study results to strengthen hazard evaluations, and should be used by EPA with appropriate considerations of study quality etc." "Zhang et al 2009 propose a biologically plausible mechanism for leukemia as follows: "formaldehyde may act on bone marrow directly or, alternatively, may cause leukemia by damaging the hematopoietic stem or early progenitor cells that are located in the circulating blood or nasal passages, which then travel to the bone marrow and become leukemic stem cells." Where the EPA Draft states that, "No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution..." (p. 54) this statement - and sentiment- should be corrected to note the proposed mechanism of Zhang et al 2009."			
"The opaque and inconsistent process of evidence integration in the 2022 Draft Assessment is exemplified in EPA's treatment of the evidence for nasopharyngeal cancers (NPCs) relative to lymphohematopoietic malignancies. In both cases, EPA concluded that the 'evidence demonstrates' that formaldehyde inhalation causes NPCs and myeloid leukemia, 'given appropriate exposure circumstances.' However, the body of evidence for these two cancers are quite different and based on EPA's own criteria, should not have the same hazard determination...In the case of NPCs, nasal tumors occur in animals and there are plausible MOAs that have supporting evidence (primarily, cytotoxicity and regenerative proliferation) to support the epidemiological findings. In contrast, myeloid leukemia has no positive animal evidence nor biologically plausible MOA." "EPA's 2005 Guidelines indicate that meta-analysis can follow systematic review and can be helpful when varying degrees of risk or conflicting results are present. A meta-analysis by Mundt et al. (2021) indicates the descriptor "Inadequate information to assess carcinogenic potential" should be used until a meta-analysis that separately analyzes AML (with control for tobacco smoking) and CML is conducted by EPA solely under its 2005 Guidelines."	ACC (0083b; 3) ACC (0100; 1, 6, 7, 22, 29, 43) ACC (0103; 15-20, 30-31, 33-34, 48-53) ACC (0083a; 6-7)	6c, 6e, 6f, 7, 1a, 1b,	*Myeloid leukemia*

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"The experimental evidence in animals on formaldehyde inhalation was incorrectly assessed in the Draft Assessment, leading to an inaccurate determination that 'the evidence available from animal studies is considered indeterminate for drawing conclusions as to whether or not formaldehyde exposure might cause leukemia or lymphoma.' Formaldehyde is one of the most-studied chemicals in the world. Reflecting this, eleven cancer bioassays have been performed with formaldehyde (that have recently been reviewed by Thompson et al., 2020), via the inhalation route: seven in rats, two in mice, and two in hamsters. A complete animal experimental database in laboratory animals is often considered to consist of chronic bioassays in two species, which clearly formaldehyde exceeds. If the formaldehyde cancer bioassay database is considered indeterminate, then virtually no experimental database can meet the bar set in the Draft Assessment. We disagree with the low rating of the overall study quality of the database in the Draft Assessment. Notably the Draft Assessment rated one rat cancer study (Table 1-65) and one mouse cancer study as "high confidence" studies, clearly meeting the EPA definition of a complete database for assessing formaldehyde carcinogenicity. Thus, it is unclear why his database was considered "indeterminant" in the Draft Assessment. Neither of the two high confidence studies identified a treatment-related increase in leukemia; their exclusion from integration into the assessment of leukemogenic potential prevents the Draft's conclusions from reflecting best available science." "In synthesizing the results of the epidemiology studies, EPA emphasized consistency, magnitude of effects, and dose-response gradients. For example, the EPA reported 'consistent increases in risk across a set of high and medium confidence, independent studies with varied study designs and populations.' The estimates of relative risk of myeloid leukemia, however, were not consistent within or between studies in relation to various formaldehyde exposure metrics…A conclusion of consistent associations between formaldehyde exposure and myeloid leukemia is not scientifically justifiable when the observed associations between formaldehyde measures and myeloid leukemia differ according to exposure metrics between studies (that is, consistency is not met when one study reports an association with peak exposure but not cumulative exposure, while another study reports an association with cumulative exposure but not peak exposure)." "The scientific evidence does not support EPA's conclusion that 'evidence demonstrates' formaldehyde causes myeloid leukemia. In the 2022 Draft assessment, EPA concluded that 'the evidence demonstrates that formaldehyde inhalation causes myeloid leukemia in humans given appropriate exposure circumstances'[90] This conclusion mirrors the conclusion in the 2010 Draft Assessment. In its revised assessment of lymphohematopoietic (LHP) malignancies, EPA no longer categorizes LHPs as one large group, as recommended by NASEM (2011). EPA, however,			

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continues to lump two distinct cancers -- acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), into myeloid leukemia." "The 2022 Draft Assessment concludes that the human evidence for myeloid leukemia is 'robust' based on 'consistent increases in risk across a set of high and medium confidence… studies…strong associations…and…temporal relationship[s] consistent with causality.'[50] However, setting aside the inappropriate grouping of acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), the body of epidemiological evidence on myeloid leukemia does not provide 'robust evidence' of an association – it is neither consistent nor strong. Specifically, epidemiological studies of occupational groups historically highly exposed to formaldehyde generally do not demonstrate statistically significantly increased rates of myeloid leukemia or more specifically AML and CML: 1. No statistically significant excess risk above background rates of myeloid leukemia is reported in the three myeloid leukemia studies rated as having "effect estimates classified with high confidence" (Hauptmann et al., 2009; Beane Freeman et al., 2009; Meyers et al. 2013). 2. Results from studies with as high or higher quality observed no significant increases in AML, CML, or myeloid leukemia (Saberi Hosnijeh et al. 2013, Talibov et al. 2014, Checkoway et al. 2015). 3. Results do not indicate consistent excesses across exposure measures in the studies rated "high confidence" (Hauptmann et al., 2009; Beane Freeman et al., 2009; Myers et al. 2013). Overall, there is no 'reasonable confidence that alternative explanations' (i.e., chance) can be ruled out." "Given that EPA acknowledges in the 2022 Draft Assessment that there are no known MOAs for formaldehyde and lymphohematopoietic malignancies, EPA should have deprioritized these malignancies for assessment." "The Draft Assessment inappropriately combines myeloid and other/unspecified leukemias together into one class which it then refers to as "myeloid leukemia (p. 2-87) contrary to the NAS (2011) recommendation against combining incidence of different leukemia types." "NASEM has consistently recommended improvements to the evidence integration process, including its transparency. Evidence integration should focus on outcomes or endpoints with robust evidence and fully consider study quality. This should include consideration of MOA. As detailed further below, the 2022 draft does not fully meet this recommendation, particularly with respect to lymphohematopoietic malignancies. EPA concluded 'evidence demonstrates'			

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that formaldehyde inhalation causes myeloid leukemia in humans, despite the weak human evidence, lack of evidence in animal studies, and lack of a biologically plausible MOA." "There is compelling evidence that inhaled formaldehyde is 1) not systemically distributed at ≤15 ppm, precluding a direct mutagenic MOA; and 2) not leukemogenic in animal models, including transgenic models designed to be sensitive for detecting leukemogenic effects. The Draft Assessment, however, sets aside the evidence that does not support a leukemogenic effect. Rather, the Draft Assessment concludes that formaldehyde is a known human leukemogen, based solely on a non-statistically significant numerical association inconsistently observed in epidemiology studies. This is not reflective of data integration, causal determination based on weight of evidence, or sound science." "There is no established plausible mode of action for myeloid leukemias. • EPA continues to rely on flawed studies purportedly demonstrating an MOA. • EPA's speculations on potential MOAs for myeloid leukemia lack evidence and therefore biological plausibility. • EPA fails to consider Gentry et al. (2020) in assessing the biological plausibility of a causal association between inhalation of formaldehyde and myeloid leukemia" "Failure to fully integrate evidence in this manner, along with numerous other limitations in EPA's synthesis of the epidemiological evidence, are discussed in detail in the sections that follow. They can be broadly summarized as follows: • EPA lumps together myeloid leukemias, failing to differentiate between AML and CML, which have very distinct genetics and risk factors. • EPA fails to truly weigh and integrate the available evidence: it inappropriately downgrades and dismisses important re-analyses and studies, including Checkoway et al. (2015), which are highly informative regarding formaldehyde and LHP malignancies. • EPA raises up flawed studies such as Hauptmann et al (2009). • EPA mischaracterizes and overemphasizes risk estimates for purported peak exposure metrics relative to cumulative exposure metrics, which are consistently null." "Since the NAS (2011) review, more definitive data on the lack of systemic distribution of inhaled formaldehyde have become available (Lu et al., 2011; Moeller et al. 2011; Edrissi et al. 2013, 2017; Yu et al. 2015; Lai et al., 2016; Leng et al., 2019). It is noteworthy that the more recently published peer-reviewed literature provides further support for the conclusions reached by the NAS (2011) that there is a lack of causal evidence Such evidence on causality, or the lack thereof, was recently assessed by Gentry et al. (2020) using the IPCS MOA framework.			

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They concluded that LHPs are highly unlikely to be directly related to inhalation of formaldehyde." "The Draft Assessment maintains problematic conclusions on systemic genotoxicity/mutagenicity in circulating blood cells. The Draft Assessment continues to conclude that a mutagenic MOA is operable for systemic effects, despite conclusive evidence that formaldehyde is not systemically distributed after inhalation, at environmentally relevant concentrations. It is hard to understand why the EPA continues to conclude that a potential biomarker of a mutagenic effect on circulating blood cells, that is not dose-responsive, supports a linear low-dose leukemogenic response, when EPA has previously and repeatedly been advised this approach is problematic." "As discussed in these comments, EPA relies heavily on just a few flawed studies (Zhang et al. 2009, 2010; Lan et al. 2015) which 'reported effects on myeloid progenitor cells cultured from peripheral blood of exposed workers compared to cells cultured from controls without occupational formaldehyde exposure.'[58] These studies have since been refuted in the literature (Mundt et al., 2017." "Furthermore, a direct genotoxic effect on the bone marrow, resulting in an impact on circulating cells, has been all but disproved by several studies published after Zhang et al.'s (2010) initial study including Lu et al. 2011, Moeller et al. 2011, Yu et al. 2015, and Lai et al. 2016. These studies show that due to the reactive nature of formaldehyde, exogenous formaldehyde is not able to move beyond "the portal of entry" (Mundt et al. 2017)." "Furthermore, there is ample literature examining whether formaldehyde might cause mutations leading to cancer in blood progenitor cells. Drs. Albertini and Kaden note in their comment on the 2022 Draft Assessment that EPA failed to include two of their papers: • Albertini RJ, Kaden DA. 2016. Do chromosome changes in blood cells implicate formaldehyde as a leukemogen? Critical Reviews in Toxicology, 47(2): 145-184. • Albertini RJ, Kaden DA. 2020. Mutagenicity monitoring in humans: global versus specific origin of mutations. Mutation Research/Reviews in Mutation Research, 786: 108341." "EPA mistakenly assumes that biomarkers of exposure (or even effect) in circulating blood cells are the same as genotoxicity in target cells." "The Draft Assessment still considers indirect biomarkers of systemic genotoxicity as evidence supporting a genotoxic MOA. The Draft Assessment uses this mechanism to support the hypothesis of cytogenetic effects in circulating blood cells and calculate a linear IUR for leukemia in the absence of any dose-response observations for leukemia or demonstration of			

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in vivo genotoxicity. The approach taken in the Draft Assessment clearly does not follow or adequately address the NAS comments above." "For example, in the highly influential National Cancer Institute (NCI) cohort study (Beane-Freeman et al. 2009), the strength and specificity of the exposure-response associations varied considerably over the period in which the cohort was followed. In addition, the reliance on the peak-exposure metric to determine causality in that study rather than the more conventional dose metric of cumulative exposure should be further justified, particularly in the absence of established modes of action.[44]" "... the draft concludes that that the strength of the human evidence for myeloid leukemia is "robust" based on "several" studies with consistent findings. EPA's conclusion is based largely on the Beane Freeman analyses of the NCI cohort (pg. 1-542). EPA did not appropriately integrate apparently conflicting findings in the older epidemiological studies (Hauptman et al. (2009) funeral workers study, Beane Freeman et al. (2009) analysis of the NCI cohort) with the analyses published more recently, which demonstrate no excess in cancer risk (e.g., Checkoway et al. (2015) re-analysis of the NCI cohort). EPA should re-examine its evaluations of study confidence (and risk of bias, especially including statistical analyses) and more fully integrate and interpret the earlier studies in the context of the broader body of more informative and updated studies." *[Please see docket for details and supporting information]*			
"The classification of 'evidence demonstrates' that formaldehyde causes myeloid leukemia is not supported and should be reevaluated based on the growing amount of information which argues against a causal association. Based on EPA guidelines (Table 8 of EPA, 2022a), the classification of 'evidence suggests' is more appropriate given the conflicting and inconsistent findings in human epidemiological studies, the indications of chance, bias and confounders in key positive epidemiological studies, the consistent lack of statistically significant associations, negative animal studies, and the lack of mechanistic evidence supporting a mode of action." *[Please see docket for details and supporting information]*	LCA (5)	6c	*Myeloid leukemia*
"In support of leukemia and genotoxicity, the U.S. EPA acknowledges the lack of systemic delivery but then invokes non-specific local mechanisms causing systemic genotoxicity. These views are in direct contrast to other organizations. For example, the OECD test guideline 474 for in vivo micronucleus induction requires proof of systemic delivery of a test article when negative genotoxicity results are to be accepted for regulatory purposes.[3] This implies that the genotoxicity experts who designed the test guidelines anticipate that genotoxicity in distal tissues requires systemic delivery of the test article. The doses in these guideline studies typically include a maximal tolerated dose that would presumably elicit local effects that would,	ToxStrat (9-12)	6c	*Myeloid leukemia*

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if capable of inducing systemic genotoxicity, interfere with the interpretation of the test results. Since indirect genotoxicity mechanisms are not accounted for in guideline tests, it can be surmised that genotoxicity experts do not consider local effects a capable or meaningful contributor to systemic genotoxicity. Additionally, the purpose of genotoxicity testing guidelines and [a]s acknowledged by the NRC and U.S. EPA, inhaled formaldehyde is not systemically distributed up to 15 ppm. As such, the likelihood that local effects are inducing systemic genotoxicity is low. Data from ADH5 null mice (see above) indicate that even 2-fold increases in serum formaldehyde levels do not cause genotoxicity. Given EPA's hypothesis that elevated formaldehyde at the portal of entry might cause inflammation or oxidative stress, one might assume that ADH5 null mice, having elevated formaldehyde in all tissues, would have higher levels of oxidative stress and DNA damage, yet this does not appear to be the case." "Table 35 also lists as indirect support for genotoxicity 'strong and consistent evidence of mutagenicity (increased incidence of MN, CA, and chromosomal aneuploidies) in PBLs of human workers'. Elsewhere in the assessment, U.S. EPA acknowledges that inhaled formaldehyde does not distribute beyond the site of contact. As such, U.S. EPA must believe that these data indicate that there is strong and consistent evidence that low levels of inhaled formaldehyde are potent enough to induce systemic genetic damage through indirect mechanisms. Given that many scientists might find this difficult to believe, it is incumbent on the U.S. EPA to strengthen their position…However, U.S. EPA does little to bolster their conclusions. For example, there is no attempt to evaluate their conclusions vis-à-vis the controlled studies by Speit et al. (2007) and Zeller et al. (2011). U.S. EPA could bolster their conclusions by identifying other chemicals with strong experimental data demonstrating that inhalation exposure results in systemic genotoxicity without systemic delivery of the parent compound or metabolites; however, no such discussion was found…" "In a subsection of 1.2.5 on page 1-303 it is stated that "long-term occupational exposure was associated with significantly increased MN in PBLs, and aneugenicity appears to be the predominant effect in peripheral tissues (see Section 1.3.3)." There are three problems in this one sentence. First, the U.S. EPA is referring to information supporting URT carcinogenicity that has not yet been discussed. This makes following their arguments unnecessarily difficult. Second, why would formaldehyde genotoxicity be associated with long-term exposure but not shorter-term exposure? Formaldehyde does not bioaccumulate and data indicate that formaldehyde-related adducts are labile. Similarly, if the damage were due to oxidative stress or inflammation, these too are transient effects that likely resolve. Skipping ahead to section 1.3.3 I found no explanation; moreover, if there is an explanation in the document it should be recapitulated whenever such data are used to support MOA. The third issue with the above			

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quote is that U.S. EPA states that aneugenicity appears to be the predominant form of genotoxicity in peripheral blood lymphocytes. Considering that aneugenicity is broadly regarded as a threshold form of genotoxicity, it is curious why low-dose linear extrapolation was conducted. Again, I skipped ahead to section 1.3.3 but found no discussion on the implications of aneugenicity for low dose extrapolation. However, on page 1-524 U.S. EPA concludes that formaldehyde cause aneuploidy in PBLs and clastogenicity in nasal tissues. Notably, Speit et al. (2011) reported that formaldehyde induced clastogenicity but not aneugenicity in cultured cells. Taken together, the reported associations between formaldehyde inhalation exposure and aneugenicity in worker PBLs suggests that such observations are due to something other than formaldehyde exposure.”			
"The EPA largely disregarded the Mundt et al. (2017) fuller analysis of the Zhang et al. (2010) data...Mundt et al. (2017) requested the exposure data via an NCI Technology Transfer Agreement and was provided the average of the three exposure measures for each exposed worker, but not the individual measurements. Thus, the true range of exposure measurements could not be determined. However, they were able to evaluate the relationship, if any, between the average of the individual formaldehyde exposure measurements and all blood and genetic aneuploidy results (Mundt et al. 2017). These results demonstrated no correlation between formaldehyde exposure level (reportedly over at least a fourfold range) and any of the blood or aneuploidy results. Furthermore, the few assay results generated by tests that met the study protocol (e.g., numbers of cells counted, as pointed out by Gentry et al. (2013) appeared to be related to smoking (but not formaldehyde). " "Overall, the 2022 Draft does not fully consider or integrate the findings of the fuller analyses that call into question Zhang et al. (2010)’s findings nor does it appropriately integrate evidence from cohort studies reporting ML (and specifically AML) results. The fact remains that there are no studies supporting a MOA for formaldehyde causing leukemias (including AML) and there are several key findings that detract from this hypothesis, e.g., 1) formaldehyde does not form either DNA: protein crosslinks or DNA adducts in bone marrow, 2) exogeneous formaldehyde does not escape the portal of entry, 3) there remains no consistent statistically significant relationships between formaldehyde exposure and chromosome aberrations, sister chromatid exchanges or micronucleated cells in hematopoietic stem cells as conducted in animals, 4) studies in humans exposed to formaldehyde have failed to find a relationship between exposures and chromosomal changes in peripheral blood lymphocytes and 5) the available epidemiological evidence is consistent with no significant increase in LHM, specifically AML, among formaldehyde-exposed workers."	Cardno (0095; 3, 5-7)	6c	*Myeloid leukemia*

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"The EPA 2022 Draft Report continues to rely on a cross-sectional study to support a possible MOA for an association between inhalation exposure to formaldehyde and LHMs, based on what they claim (even in the title of the paper) to be "leukemia-specific chromosome changes in cultured myeloid progenitor cells" (Zhang et al. 2010). Cross-sectional studies are incapable of demonstrating changes in clinical markers but might reflect underlying differences between compared groups." "Additionally, the 2022 Draft does not integrate the fuller analyses of the Zhang et al. (2010) data with results of other studies reporting no exposure-dependent differences in blood parameters and genetic markers of formaldehyde-exposed relative to unexposed workers and other cytogenic studies (Casanova-Schmitz et al. 1984; Heck & Casanova, 2004; Lu et al. 2010)or studies examining chromosomal changes in peripheral blood lymphocytes (Bauchinger & Schmid, 1985; Cheotarev et al., 1986; Pala et al., 2008; Suruda et al., 1993; Thomson et al., 1984; Ying et al., 1999) or cytogenetic studies which show genotoxic effects, but fail to show effects on hematopoietic stem cells (He et al., 1998; Shaham et al., 2002; Yager et al., 1986; Ye et al., 2005). These studies largely align with the results of Mundt et al. (2017) and challenge the interpretation that exposure to formaldehyde may induce chromosome or genotoxic changes in blood or chromosomes." *[Please see docket for details and supporting information]*			
"The EPA mischaracterized the findings of the reanalysis of the NCI cohort study by Checkoway et al. (2015) and downgraded the exposure assessment without consideration of the issues with the peak exposure definition in the Beane Freeman et al. (2009) analysis of myeloid leukemia (addressed in Checkoway et al. 2019)…" "EPA misinterpreted the impact of defining an absolute peak exposure metric on the study findings…." "The EPA assigned low confidence to the exposure assessment in Checkoway et al. (2015) due to purported information bias and low sensitivity and suggested that the direction of expected bias would be toward the null, representing an underestimation of the actual risk. In fact, there is no such evidence of a bias toward the null in the reanalysis…" "We also published a comprehensive review of approaches to characterizing peak exposures and deriving cancer potency values from the epidemiological literature. Our analysis included nine epidemiological studies of environmental chemicals classified as carcinogens, including formaldehyde (Checkoway et al., 2019). This analysis provides additional valuable information that EPA should have considered and incorporated when evaluating the Checkoway et al. (2015) analyses conclusions to inform its approach to quantitative cancer potency characterization in the 2022 draft IRIS. Specifically, in addition to succinctly summarizing the	UCSD (1-4)	6c, 1	*Myeloid leukemia*

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results of the Checkoway et al. (2015) analysis, it also identifies issues with the characterization of peak exposure in in a case-control study of embalmers (Hauptmann et al. 2009). Furthermore, Checkoway et al. (2019) identified a pattern of limitations associated with using peak exposure data from epidemiological studies of seven additional substances (benzene, trichloroethylene, acrylonitrile, ethylene oxide, methylene chloride, styrene and/or butadiene) to inform risk characterization. Thus, the lack of a uniform approach is a critical issue that is not limited to formaldehyde. These methodological challenges include variability in peak exposure definitions across studies, lack of direct peak exposure measurements and reliance on expert judgement for exposure classifications, and potential exposure misclassification. The 2022 draft IRIS should have referred to this paper to better understand the limitations of the underlying formaldehyde epidemiological literature particularly with respect to the characterization of "peak" exposures to formaldehyde in some studies. Perhaps most importantly, the Checkoway et al. (2019) analysis substantiates the findings of Checkoway et al. (2015). The clear lack of an association with myeloid leukemia and its subtypes (AML and CML) in relation to cumulative exposure (the default exposure metric in epidemiologic studies based on its incorporation of both intensity and duration of exposure) do not support a causal association at any exposure level (Checkoway et al., 2015)." *[Please see docket for details and supporting information]*			
"The IRIS Draft failed to provide adequate evidence to support proposed mechanisms for leukemia, given the fact that inhaled formaldehyde is not systemically distributed at concentrations ≤15 ppm...The study [Lu, Collins, et al. 2010b] demonstrated that exogenous formaldehyde resulted in DNA adducts in rat respiratory nasal mucosa, but did not form [13CD2]-adducts in distant organs remote to the portal of entry. Therefore, the finding provides strong evidence to support a genotoxic and/or cytotoxic MOA for the carcinogenesis of inhaled formaldehyde in respiratory nasal epithelium, but provides evidence against the biological plausibility of inhaled formaldehyde causing leukemia or other systemic effects...The EPA IRIS Draft mentioned several possible mechanisms leading to leukemia from formaldehyde exposure, such as 'Formaldehyde-induced DNA damage to peripheral blood leukocytes', 'formaldehyde-induced systemic oxidative stress', 'formaldehyde-induced changes in the bone marrow niche', etc. However, these hypothesized mechanistic events are not supported or severely confounded by other factors." "Recommendation: The EPA IRIS Draft should provide direct evidence, rather than hypothesis in identifying the mechanisms responsible for leukemia. Further animal exposure studies are warranted to examined whether EPA hypothesized mechanistic events are supported by data, or not, before integration into a weight-of-evidence determination."	UNC (11-31)	6f	*Myeloid leukemia; Cancer MOA*

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"The IRIS Draft did not demonstrate adequate understanding of the chemistry underlying formaldehyde reactions with DNA and protein...The EPA IRIS Draft recognized the formation of protein adducts by stating that 'Formaldehyde can interact with macromolecules...or protein adducts, such as N6-formyllysine.' or 'Formaldehyde has been shown to bind to histones and chromatin forming N6-formyllysine'. This may exemplify that the EPA IRIS Draft had no adequate understanding of chemistry underlying formaldehyde reactions with DNA and protein. N6-Formyllysine is by no means a major and highly relevant protein adduct induced by formaldehyde. I and others have demonstrated that Schiff base on lysine residue is the predominant protein adduct induced by formaldehyde...Protein binding has significant impact on the formation of DNA adducts induced by exogenous formaldehyde exposure. For example, we have demonstrated that protein binding can determine the available amount of exogenous formaldehyde to target DNA to form DNA adducts...The EPA IRIS Draft did not provide any perspective on how protein binding would affect the fate of exogenous formaldehyde across tissue space... as my colleagues and I have demonstrated that inhaled formaldehyde at low doses (300 ppb and below) does not induve exogenous DNA adducts even in nasal epithelium. Then, how could exogenous formaldehyde further traverse the epithelium and enter deeper components of the tissues, such as NALT, to induce leukemia?" "Recommendation: EPA needs to revise the IRIS Draft to develop more thorough understanding of chemistry underlying formaldehyde reactions with DNA and protein and how formaldehyde-specific chemistry, such as protein binding, may affect the fate of formaldehyde across tissue space to better support evidence-based formaldehyde risk assessment. Further experiments would be warranted to examine protein binding across tissue space."			
"The IRIS Draft misinterpreted the findings of our critical, highly human exposure relevant low dose 28-day study, that precludes a mutagenic MOA at concentrations </=0.3 ppm...The EPA IRIS Draft commented that 'However, in a more recent study with a lower detection limit for adducts and testing lower formaldehyde exposure levels, Leng et al. (2019) did not observe an increase in exogenous hmDNA adducts or DPXs, including in nasal and respiratory tissues as well as at systemic sites (e.g., bone marrow), at formaldehyde levels of 0, 1, 30, or 300 ppb (up to 0.37 mg/m3) after exposure for 28 days.' Certainly, there is a difference between 'not observe an increase' in the EPA IRIS Draft and 'exogenous adducts were not detectable' as my colleagues and I reported...I appreciate that the EPA IRIS Draft acknowledged that our low dose study is helpful in improving understanding of DPX formation by stating 'The lack of detectable exogenous adducts in the URT at 0.3 ppm (0.37 mg/m^3) helps to inform the evolving understanding of formaldehyde-induced DPX at lower concentrations, which would benefit from additional study.' However, EPA IRIS Draft did not explain what additional study would be			

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needed...The EPA IRIS Draft failed to provide reasonable explanations or discuss why no exogenous formaldehyde induced DNA adduct or DPC was detected at low doses." "Recommendation: Considerably more weight-of-evidence should be assigned to our critical, low dose study. The absence of exogenous DNA adducts/DPC in any tissue, against a background of endogenous formaldehyde over 3,000x higher than the detection limit, should be interpreted in the context of interactions between formaldehyde and protein/DNA, formaldehyde carcinogenicity and the potential for genotoxicity in the absence of DNA exposure. Further clarification on 'additional study' is warranted." "The IRIS Draft showed misunderstanding of formaldehyde-induced DNA-protein crosslinks and its role in formaldehyde carcinogenicity...The EPA IRIS Draft stated that 'While some DPXs may undergo hydrolysis to form N2-hmdG adducts following exogenous formaldehyde exposure, other DPXs appear to be quite stable in vivo; it may be these latter DPXs that play a more important role in formaldehyde-mediated respiratory tract mutagenicity and carcinogenicity.' However, there is no data to support that Cys-CH2-dG is more important than Lys-CH2-dG in formaldehyde mutagenicity and carcinogenicity...Likewise, the EPA IRIS Draft states that 'the inability to detect 13C, d2-N6-hmdA was surprising, since 13C, d2-N2-hmdG is reliably quantifiable following low levels of exposure, and increases in an exposure-dependent manner in both rodents, and nonhuman primates (Yu et al., 2015b; Swenberg et al., 2013); the reason for the apparent absence of 13C, d2-N6-hmdA adducts formed by reaction with exogenous formaldehyde remains unknown.' Statements like this again may reflect the lack of adequate understanding of the chemistry underlying formaldehyde reactions with DNA and protein." Recommendation: EPA develops adequate understaning of the formation and fate of formaldehyde-induced DPC and revises the IRIS Draft to address the inaccuracy or mischaracterization in the current EPA IRIS Draft." *[Please see docket for details and supporting information]*			
"We recently reviewed the US Environmental Protection Agency (USEPA) draft evaluation of noncancer endpoints in the Draft document "Toxicological Review of Formaldehyde—Inhalation" and were dismayed to find that two of our recent papers were not considered in your assessment. The first paper, "Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?" addresses an important topic with respect to the USEPA conclusion that formaldehyde can cause myeloid leukemia. It is a comprehensive review of genotoxicity studies of formaldehyde, seeking in vivo evidence in support of the biological plausibility of formaldehyde's role in the induction of leukemia. In this review, we conclude that although chromosome-level genetic effects, as manifest as chromosomal aberration, or micronuclei	Ram (0079; 1-2) Ram (0074; 1)	6e, 6f	*Myeloid leukemia* EPA Note: Reviews and studies with no primary data are considered as supplemental materials and tracked in HERO.

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formation, in peripheral blood lymphocytes, may be positively associated with the subsequent development of cancer, even when these effects are induced in non-target tissues such as peripheral blood lymphocytes (PBLs). There is no implication of causation in these association studies. The association may simply be due to host susceptibility to developing chromosome aberrations, even those that occur spontaneously. This is consistent with mechanisms of cancer development, in which chromosomal-level mutational changes are important key events in cancer induction. Note, these chromosome-level mutational events in PBLs are independent markers of cancer risk, and not the cause of the subsequent cancer - which occur in the target organ (e.g. the bone marrow niche). Elevated frequencies of chromosomal aberrations or micronuclei in PBLs of workers exposed to formaldehyde therefore do not implicate formaldehyde as a leukemogen, and the use of these studies to suggest that they do is a misinterpretation of those studies. The second paper, "Mutagenicity monitoring in humans: global versus specific origin of mutations," is more indirectly relevant to the USEPA draft report, but nevertheless important. It addresses what in vivo mutation monitoring tells us about the target organ of origin. Assays examining genotoxicity in circulating PBLs in adults do not necessarily reflect a bone marrow origin, and in all likelihood reflect changes occurring in the periphery e.g. circulating blood or peripheral tissues. In newborns and young infants or in rare cases of hematopoietic disorders where the genetic change originated in the bone marrow, the frequency of such alterations in the circulating blood cells would be expected to be 100-fold or more over background, as seen in the few unusual cases discussed in our paper. This second paper extensively reviews the kinetics of blood cells, and illustrates why chromosome changes measured in PBLs in adults do not implicate the bone marrow in their genesis in normal adults. To equate chromosome mutations in rodents with those in humans is to conclude that the mechanism that induces leukemia in the former are also present in the latter. This conclusion is faulty because rodent experimental studies typically measure the aberrations in bone marrow while human observational studies do so in PBLs. By ignoring this critical difference, the EPA fails to recognize that current technology allows routine measurement of bone marrow chromosome mutations in humans by using the reticulocyte micronucleus assays. Results of such studies would allow a critical evaluation of the ability of formaldehyde to induce chromosome mutations in bone marrow cells - something that should be a requisite before concluding that it does." "Although the Zhang et al. (2010a) study has been widely interpreted to suggest the in vivo origins of aneuploidy or initiating genomic instability, the protocol used in this study as well as the underlying data do not support this interpretation. Instead, the data supports aneuploidy arising during in vitro expansion."			

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"While this publication [McGregor et al. 2006] was included, a similar publication on which I am the primary author (Gentry et al. 2020; reference provided below), was not included. The Gentry et al. (2020) publication also applied the IPCS human framework for the analysis of the MOAS that have been postulated for the development of leukemia following formaldehyde inhalation. The integration of the available science for formaldehyde in this publication not only demonstrated the limited amount of data that support any hypothesized MOAS, it also demonstrated the significant amount of research supporting the null hypothesis that there is no causal association between formaldehyde inhalation exposure and leukemia. Further, these analyses increase confidence in the conclusion that there is a lack of biological plausibility for a causal association between formaldehyde inhalation exposure and leukemia... Based on the inclusion of the McGregor et al. (2006) study, I would have expected the consideration of the results of the Gentry et al. (2020) study in the current Draft IRIS Assessment. The science presented in this publication is critical in the determination of the lack of biological plausibility of a causal association between inhalation of formaldehyde and myeloid leukemia and should be considered in finalizing the Toxicological Review of Formaldehyde."			
Charge Question 7: Cancer Inhalation Unit Risk			
"The inhalation unit risk (IUR) for BPC was developed using the NCI cohort study (Beane Freeman et al., 2013) as "it is the only one with sufficient individual exposure data for dose response modeling" (EPA, 2022a). The weak and inconsistent associations, methodological issues, and external confounders of the study are mentioned above and are discussed in detail in the cited references. The IUR for NPC is based on a mutagenic mode of action (MOA) which assumes a linear non-threshold (LNT) dose response (EPA, 2005). The available science does not support the use of a LNT assumption to estimate toxicity criteria for formaldehyde, a chemical which EPA acknowledges has a mixed MOA and evidence of non-linear dose response relationships (EPA, 2022a & b)." "EPA applied age-dependent adjustment factors (ADAFs) to develop the UR for NPC which is typically done for chemicals with a mutagenic MOA. However, EPA acknowledges that the carcinogenicity of formaldehyde can be attributed only in part to a mutagenic MOA. The scientific defensibility of applying ADAFs to the toxicity criteria for a chemical known to have a multi-faceted MOA, non-linear dose-response relationships, and an effect threshold is questionable." "The 2022 NPC IUR is 1.1 x 10^{-5} per µg /m^3 (1.1 excess cancer cases are expected to develop per 100,000 people if exposed daily for a lifetime to 1 µg/m^3). The overall confidence level of EPA in the NPC IUR is medium based largely on 'The small number of cases that contributed to the	LCA (8-10)	7a	*Upper respiratory tract cancers IUR*

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statistical analysis and resulting imprecision in modeling the shape of the dose-response curve' (EPA, 2022a). The 2022 NPC IUR is similar to the 1991 IUR of 1.3×10^{-5} based on nasal squamous cell carcinomas in F344 rats (EPA, 2022a)." *[Please see docket for details and supporting information]*			
"With regard to nasal tumors, there is substantive evidence indicating these tumors are the result of cytotoxicity and regenerative proliferation. In its derivation of IURs based on animal data, EPA presents an analysis of potential threshold-like effects (i.e., an RfC based on cellular proliferation). Ultimately, however, EPA concludes that because the formaldehyde-induced tumors could not solely be attributed to cell proliferation and that the evidence "at least in part" supported a mutagenic MOA, a linear no-threshold approach was supported. However, the existence of multiple MOAs does not preclude EPA from deriving toxicity values based on threshold-like responses. In the case of formaldehyde, if genotoxicity were to occur, it is expected only above those exposures associated with regenerative cell proliferation, as noted by the ECHA RAC Committee (2020) quoted above. Given the robust scientific evidence that the non-genotoxic MOA predominates and would be protective of any other MOA for carcinogenicity, EPA should consider assessing formaldehdyye nasal cancer potency using a threshold approach, rather than a linear, no-threshold IUR." "The Draft Assessment concludes that a mutagenic MOA is operative for nasal tumors and, therefore, low dose linear extrapolation is required and fails to integrate data demonstrating that both the tumorigenic response and exposure to the molecular target (i.e., DNA) are highly non-linear." "The draft Formaldehyde Review does not mention the MOA evaluation by Thompson et al. (2020). This analysis of the dose-response indicates there is a threshold for genotoxicity and that it is higher than the threshold for nasal tumors. As such, a threshold approach based on nasal tumors in rats would be protective for any tumors resulting from genotoxicity. The MOA information, together with the robust toxicity database for formaldehyde, provides ample evidence to "justify a conclusion that mutagenicity is not operative at low doses and focus on a non-linear approach," in accordance with the 2005 Guidelines. In addition to the updated MOA by Thompson et al. (2020), authoritative sources have concluded there is a threshold for both nasal tumors and genotoxicity: i. ECHA Committee for Risk Assessment (RAC). 13 March 2020. Opinion on an Annex XV Dossier Proposing Restrictions on Formaldehyde and Formaldhyde Releasers...ii. WHO. 2010. WHO Guidelines for Indoor Air Quality: Selected Pollutants. World Health Organization, Regional Office for Europe." "Concordance of effects and other information that supports a threshold MOA, supported by dosimetry was excluded from the assessment. Understanding that the nasal tumors form only	ACC (0083a; 7-8) ACC (0103; 7, 58) ACC (0100; 5, 32, 52-54, 56) ACC (0083b; 6)	7a, 6f	*Upper respiratory tract cancers IUR; Cancer MOA; "Bottom-up" approach*

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at exposure levels at which normal homeostasis has been upset is a critical point in apprehending why a threshold is observed in tumor response. These data [Thompson et al. 2020; Anderen et al. 2010] argue strongly against the use of low dose linear extrapolation into the zone of homeostasis (below background levels of endogenously produced formaldehyde)." "EPA's carcinogenicity risk-assessment guidelines recommend considering alternative models, especially when biologically based dose-response models are unavailable (EPA 2005). That exercise is especially important when a single study with uncertainties associated with selected cancers and inconsistency with exposure metrics is used. Despite this guidance the Draft Assessment concludes that Formaldehyde is a Human Nasal Carcinogen that acts via a genotoxic mechanism, with a linear dose response, and excludes consideration of the cytotoxic and regenerative hyperplasia threshold MOA recently updated by Thompson et al. (2020), as an alternative MOA." "... EPA's linear unit risk estimate for NPC is essentially unchanged from the value derived over 30 years ago, despite the prodigious growth in the scientific database on formaldehyde indicating that formaldehyde is a threshold carcinogen." "Toxicodynamics and toxicokinetics considerations, demonstrating highly non-linear dosimetry, were not taken into consideration when deriving quantitative estimates of risk." "EPA's formaldehyde cancer slope factor is not based in reality. It projects that background formaldehyde levels of 5 and 20 ppb will result in 8 and 20% of the annual NPC US incidence in non-smokers, or of 16 and 40% of the population when smokers are included. Moreover, using an EPA cited background NPC incidence of 0.6 per 100,000 folks, EPA's cancer slope factor for formaldehyde, and average indoor formaldehyde concentrations, projects incidences at 20 or 51% of the annual NPC US incidence rate. These values clearly do not match the available literature, which shows minimal, if any, background NPC due to formaldehyde, nor is it consistent with highly reliable biomarker of exposure/molecular dosimetry data that indicates little to any exogenous formaldehyde entering cells at average indoor air concentrations, against a high background of endogenous exposure of the DNA. The molecular dosimetry data demonstrates that inhalation exposures could not have added risk of more than 1/3,000th of the endogenous risk. With an average incidence rate of ~2,000 per year in the US, based molecular dosimetry, at maximum formaldehyde could be causing <1 case per year of nasal cancer in a population of 300,000,000 US residents. Clearly, formaldehyde does not present an unreasonable risk of nasal cancer in the US, at average indoor air concentrations." *[Please see docket for details and supporting information]*			
"The IRIS Draft did not appreciate or misunderstood the key molecular dosimetry data using DNA adducts as the formaldehyde-specific biomarker. The EPA IRIS Draft simply used a	UNC (9-11)	7	*Upper respiratory tract cancers IUR*

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sentence to state that 'an increase in exogenous formaldehyde adducts has been observed in rat nasal tissue at 0.7–15 ppm', which clearly did not appreciate or understand the significance of the critical molecular dosimetry data set." "I appreciate that EPA agreed with formaldhyde mutagenic MOA, however, how could the IRIS Draft still perform a linear low-dose extrapolation given our clear evidence that formaldehyde interacted with DNA in a highly non-linear fashion?" "Recommendation: The EPA IRIS Draft should discuss and consider the critical molecular dosimetry data and the non-linear dose response for DNA adducts in the risk estimates for inhaled formaldehyde" *[Please see docket for details and supporting information]*			
"More importantly, if U.S. EPA believes that these are the two primary drivers of URT carcinogenicity and there is broad scientific consensus that there are exposures that do not increase proliferation and exposures that do not increase exogenous adducts, then it is perplexing that one of these apparently threshold mechanisms could not serve as a basis for an RfC protective against URT carcinogenicity. The application of uncertainty factors could account for any remaining uncertainty U.S. EPA has about where these thresholds occur in humans. Instead, U.S. EPA appears to accept every publication equally to the point of decision paralysis about whether there is any lower bound on exposures that do not result in proliferation or mutation-inducing adducts and therefore U.S. EPA defaults to linear no threshold cancer slope factor development."	ToxStrat (13-14)	7a	*Upper respiratory tract cancers IUR*
"NRDC is concerned that the risk of SNC is not given appropriate weight; it should be included, quantitatively, in the overall cancer risk calculation. As NIEHS notes, "EPA has concluded that (1) formaldehyde is genotoxic in humans (based on studies using buccal, blood, and nasal tissues from exposed humans) and in experimental systems, (2) a genotoxic mode of action plays a role in the development of nasal tumors (SNC) and NPC, and (3) there is moderate confidence for a causal association between formaldehyde exposure and SNC risk from human studies," (NIEHS p. 12). The hazard for SNC from formaldehyde is established by the existing science; failure to include it in an overall risk estimate may result in an underestimate of risk." "NRDC agrees with EPA's use of an ADAF-adjusted Inhalation Unit Risk (IUR) for NPC of 1.1×10^{-5} per ug/m^3 (0.013 per ppm) (Table 2-40, p. 721). This value represents the upper-bound estimate of the increased lifetime risk of cancer from inhaling 1 ug/m^3 of formaldehyde over a lifetime. The ADAF adjustments are to address exposure over a 70-year lifetime, which includes vulnerable periods of childhood, and are required by EPA's Cancer Guidelines because the NPC cancer is due, at least in part, to a mutagenic mode of action. (p. 58)." "NRDC is concerned that the failure to include SNC in its overall risk finding (the inhalation unit risk, IUR), which is instead based only on the risk of NPC, will result in an underestimate of risk.	NRDC (6-7)	7	*Upper respiratory tract cancers IUR*

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Excluding both SNC and myeloid leukemia risk from the calculated IUR is pretending the risks don't exist when in fact they are scientifically established hazards. NRDC suggests that EPA could instead present a range of overall cancer risk, from NPC-only to NPC and myeloid leukemia, and including SNC risks. This is more consistent with EPA policy to add cancer risks, and would provide both a scientific and policy honesty to EPA's evaluation. Providing this range of overall risk values will inform decisions by regulatory agencies at local and state levels, other countries, industry, unions, communities, consumers, and others."			
"EPA was compelled to develop a IUR estimate because of its judgement that the available 'evidence demonstrates' that formaldehyde causes myeloid leukemia. As discussed above, LCA and other groups and scientists disagree with this designation of causality due to weak or absent causal associations, inconsistent findings, no established mode of action, etc. The methodology used by EPA to develop the IUR for myeloid leukemia further demonstrates why 'evidence demonstrates' is inappropriate." "Because of the insufficient human and animal data base, EPA used exposure data for myeloid leukemia plus other/unspecified leukemias (which may include cases of myeloid leukemia but does include cases of non-myeloid leukemias) to develop the IUR. Due to the lack of data showing causal associations, EPA used exposure data that did not show an association with formaldehyde exposure. Because mechanistic data are insufficient to determine a MOA for formaldehyde induction of myeloid leukemia if it occurs, EPA used a default linear low-dose extrapolation, the shortcomings of which were presented under the discussion of the IUR for NPC. EPA (2002a) states that it used 'an innovative approach' i.e., one not yet subject to review and approval by the scientific community, to derive and present potential unit risk estimates for myeloid leukemia…EPA has developed an IUR for myeloid leukemia which seems scientifically indefensible and in which the Agency admits it has low confidence." *[Please see docket for details and supporting information]*	LCA (10-11)	7d	*Myeloid leukemia estimate*
"For leukemia dose response assessment, the Draft Assessment uses several methods, both for deriving the inhalation unit risk (IUR) factor for myeloid leukemia and for different combinations of myeloid leukemia and other types of leukemia. Each of the derived IURs, presented in Tables 2-31 through 2-25 fall within the range of 0.03 to 0.48 (per mg/m^3). No mention of relative dosimetry related to naturally occurring background concentrations of formaldehyde is included in the assessment of uncertainties in Table 2-36 or included in the section (2.2.5) of the draft assessment that was titled 'Cancer Risk Based on Background Cancer Incidence and Internal Dose of Endogenous and Exogenous Formaldehyde." "It seems that an alternative approach would be to recognize that there are considerable uncertainties in the Draft Assessment cancer risk estimates, that there is direct evidence	ACC (0100; 32-33)	7	*Myeloid leukemia estimate*

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against an association between leukemia and formaldehyde at environmentally relevant concentrations, and that the associations between formaldehyde and myeloid leukemia were not statistically significant in the study used to calculate the IUR." *[Please see docket for details and supporting information]*			
"EPA did not include all cancer endpoints in the estimated inhalation unit risk. EPA has appropriately determined that the evidence demonstrates that formaldehyde inhalation causes an increased risk of myeloid leukemia in humans. This determination is consistent with previous findings by International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP), with the NAS affirming the NTP conclusion. EPA, however, does not incorporate the quantitative risk of myeloid leukemia into its estimated inhalation unit risk for formaldehyde, saying that this exclusion is due to uncertainty in the interpretation of the modeling results. It is not appropriate to exclude myeloid leukemia from the quantification of formaldehyde cancer risk, regardless of the uncertainty. EPA's National Air Toxics Assessment (NATA) has identified formaldehyde as the largest nation-wide contributor to cancer risk from air toxics. Exclusion of myeloid leukemia from calculation of the IRIS inhalation unit risk will result in consistent underestimation of cancer risk and will adversely affect risk management decisions, particularly in over-burdened communities that experience poor health status in part because of exposure to formaldehyde and other air toxics. EPA should use the results of its best modeling efforts for myeloid leukemia risk from formaldehyde inhalation and incorporate those results into its overall estimate of the inhalation unit risk for formaldehyde. Based on the current draft, that means use of the model results using data from the National Cancer Institute (NCI) study."	UCSF (5)	7d, 7e	*Myeloid leukemia estimate*
"EDF recommends that the agency consider using the unit risk for myeloid leukemia to inform the overall cancer IUR. As stated previously, EPA did conclude that the available scientific evidence "demonstrates" that formaldehyde inhalation causes myeloid leukemia. Furthermore, as EPA stated in the Draft Assessment, the public health burden should be considered; nasopharyngeal cancer is rare and, in comparison, myeloid leukemia is more prevalent (pg. 712). EDF does not have specific recommendations for how to include the unit risk of myeloid leukemia to that of the overall cancer IUR. Rather, we ask the agency to consider the following points as it reviews comments on how to potentially update the cancer IUR. When deciding if and how the unit risk for myeloid leukemia should inform the cancer IUR, EPA should consider the existing weakness associated with the current IUR. Our specific points to consider are as follows: • Uncertainty with the exposure metric	EDF (2-3)	7e	*Myeloid leukemia estimate*

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• Potential bias associated with heterogeneity among the industrial plants included in the NCI studies The National Academies also flagged these similar concerns about the Hauptmann et al., 2004 study, which was used to derive the IUR for nasopharyngeal cancer in the 2011 draft formaldehyde assessment in its review of the 2011 document.[4] We highlight these areas of uncertainty again as we believe they would be important to consider as EPA evaluates the benefit of considering myeloid leukemia in the cancer IUR." *[Please see docket for details and supporting information]*			
"EPA acknowledges some uncertainty in the low dose-response due to the potential for endogenous formaldehyde levels to reduce the uptake of inhaled formaldehyde. Importantly, as EPA concludes, this limitation is negligent given robust scientific evidence demonstrating that formaldehyde has genotoxic, mutagenic and cytogenic mode of toxicity, thus supporting a linear low-dose extrapolation (p. 158, 171)." "NRDC urges EPA to consider applying ADAFs to the myeloid leukemia risk estimate. EPA did not apply ADAFs to this endpoint. NRDC supports the use of ADAF lifetime adjustments. NRDC joins the broad scientific community in advocating that this adjustment should be applied to all carcinogens, not just those that are mutagenic. This is done by Cal-EPA OEHHA, for example." "NRDC is concerned that the proposed IUR will strip away much-needed health protections, as it is roughly 10-fold less protective than EPA's 2010 draft risk estimate of 1.1×10^{-4} per ug/m^3 (0.13 per ppm) based on myeloid leukemia. In fact, it sets IRIS back about a quarter-century, to the 1991 cancer risk estimate of 1.3×10^{-5} per ug/m^3 that remains in the IRIS database." "NRDC disagrees with excluding the risk estimates for myeloid leukemia in EPA's overall risk estimate (the inhalation unit risk, IUR), which is instead based only on the risk of NPC. This is an especially significant oversight given that myeloid leukemia is a much more common disease than NPC, which is a very rare cancer. EPA explains its omission of the myeloid leukemia risk as due to some uncertainty and therefore a lower confidence in the exposure-response modelling results (Tox Draft p. 57). Nonetheless, the IRIS draft calculates a risk estimate for myeloid leukemia risk, of 3.4×10^{-5} per ug/m^3 (0.042 per ppm) (Table 2-35, p. 710)."	NRDC (4, 6, 7-8)	7	*Myeloid leukemia estimate*
"EPA's choice of dosimeter is wrong. EPA's own text indicates that that the choice of dosimeter for the formation of tumors, either nasal pharyngeal or leukemia, is related more to the peak concentration rather than the cumulative exposure. Thus, EPA needs to develop a low dose response extrapolation on the basis of peak exposure, despite the apparent difficultly in doing so. Otherwise, EPA's projected lifetime cancer risks are not credible." "EPA should also consider the recent findings of the Alliance for Risk Assessment (ARA) Beyond Science and Decisions workshop XIII, where formaldehyde was used as an example of a new	TERA (0078b; 6) TERA (0078a; 6-7)	7, 5	*IUR (general)*

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approach to dosimetry that may offer some insights.13 Simply put, this case study suggests that formaldehyde cannot penetrate the cell nucleus at low concentrations, thus supporting the threshold approach suggested by Thompson et al. (2020). In such cases, EPA (2005) cancer guidelines dictate the use of RfDs or RfCs as the basis of the low dose extrapolation rather than a linear low dose modeling." *[Please see docket for details and supporting information]*			
"The 2022 draft Formaldehyde Review indicates that epidemiological data are preferred for dose-response analysis and derivation of toxicity values. In many cases, the epidemiological evidence is not suitable for use in quantitative dose-response due to insufficient exposure-response information or other issues. For formaldehyde, only animal data are adequate to describe the dose-response (i.e., threshold or 'hockey-stick') relationship between formaldehyde and cancer, and these are limited to nasal cancer. Despite acknowledging the evidence for LHPs is of 'low confidence,' EPA derives an IUR nonetheless. For specific leukemias (or other specific LHM), neither the animal toxicology nor the epidemiological evidence demonstrates a clear causal relationship and therefore deriving a slope factor or unit risk for leukemia is inappropriate." "The Draft Assessment does not integrate the evidence developing IURs for nasal cancer and leukemia and fails to integrate of animal studies, toxicodynamics, toxicokinetics, or dosimetry into the modeling." *[Please see docket for details and supporting information]*	ACC (0083a; 7) (ACC 0103; 58)	7a, 7b, 7d	*IUR (general)*
"...All of EPA's and Crump et al.'s (2014) claims regarding the 'bottom-up' approach are no more than speculative 'hand-waving'. In what follows, we address and rebut these claims regarding our approach with formaldehydye-specific data." *[Please see docket for details and supporting information]*	TS (1-5)	7, 6e, 6f	*"Bottom-up" approach*
"The EPA IRIS Draft used speculations, instead of any data, to decline the adoption of the bottom-up approach that offers the opportunity to serve as an independent 'reality check' on low-dose risk estimates. The EPA IRIS Draft concluded that 'the bottom-up approach does not necessarily provide an upper bound on the slope of the dose-response at low exogenous exposures, primarily because the ratio of background tumor incidence to internal endogenous concentration at the true target tissue may underpredict the slope of the dose-response above that endogenous concentration.' The EPA IRIS Draft further stated that 'This is further discussed in Crump et al. (2014)' yet without providing any data to support such a claim in the Draft. In fact, Crump et al hypothesized in the Letter to the Editor that 'A sublinear dose–response relationship over the endogenous range is clearly plausible on biological grounds. For example, it is likely that baseline levels of DNA repair enzymes and other protective systems evolved to	UNC (41-44)	7, 6e, 6f	*"Bottom-up" approach*

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deal with endogenous DNA damage would work most effectively for lower levels of endogenous adducts.' (Crump et al. 2014) Once again, no data were provided to support such a hypothesis in either Crump et al. 2014 or the EPA IRIS Draft. Without development of data to the contrary, the approach taken by Swenberg et al. remains fully supported by existing data and is not questioned by unfounded hypotheses." "Recommendation: The EPA IRIS Draft must be revised to provide specific evidence, instead of speculations, for decision-making in terms of the utility of the bottom-up approach in low-dose risk estimates."			
"EPA should follow its own guidelines and develop a low dose cancer extrapolation based on a dual MOA. The proposed hockey-stick approach of EPA's own award winning scientist, Rory Conolly, would likely approximate the end result, but other approaches might be considered, such as that suggested by Dourson et al. (2008) for acrylamide, or published by McGregor et al. (2006) or by Thompson et al. (2020) for formaldehyde, the latter effort which was adopted by the European Union. See in particular Table 6 and Figure 8 of Thompson et al. (2020)." *[Please see docket for details and supporting information]*	TERA (0078b; 4-5)	7, 6	*Biologically based dose-response (BBDR) modeling*
"EPA's approach to the evaluation of BBDR modeling in the 2022 Draft Assessment was misguided and inconsistent with EPA's own cancer guidelines... Dr. Conolly concludes that EPA should consider the uncertainties of the BBDR model relative to the hidden uncertainties embedded in the empirical dose-response functions that they prefer, since lack of explicit description of mechanism does not avoid accountability for the mechanism, especially when so much relevant data are available... Results from [Starr and Swenberg's] evaluation are important in bounding the potential risks for cancer in consideration of the endogenous production of formaldehyde." *[Please see docket for details and supporting information]*	ACC (0103; 58)	7, 6	*BBDR modeling; "Bottom-up" approach*
"The overall formaldehyde dataset for F344 rat nasal tumors and related mechanistic information is probably the most extensive such dataset in existence for any chemical. Given that the USEPA's own Guidelines for Carcinogen Risk Assessment (USEPA 2005) clearly state a default preference for data-driven risk assessment, its multi-decade effort to develop a cancer risk assessment for formaldehyde, and its own significant resources in computational toxicology and risk assessment, it is curious that USEPA has not developed a BBDR model for formaldehyde. USEPA IRIS has, however, devoted considerable resources (Crump et al. 2008; Subramaniam et al. 2007; Subramaniam et al. 2008) to evaluate the CIIT BBDR model (Conolly et al. 2003; Conolly et al. 2004). Those of us who have developed biologically motivated models in support of risk assessment understand that no model is perfect, and that model analysis and iterative refinement support reductions in model uncertainty. It would have been interesting and informative, and consistent with their own Cancer Guidelines, if USEPA IRIS had chosen to	Ram (0075; 1-8)	7, 6	*BBDR modeling* EPA note: the 2022 draft IRIS assessment developed and presents results from alternative versions of the CIIT BBDR modeling of the rat data. However, the CIIT human BBDR model developed for

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use their analyses to develop a refined version of the CIIT model. Instead, USEPA has rejected the CIIT BBDR model and turned to more empirical approaches. In making this choice, USEPA is effectively saying that relevant mechanistic data are confusing and increase rather the decrease uncertainty, a position that is inconsistent with the 2005 guidelines. In this regard, it is worth noting that I was employed in USEPA/ORD from 2005 through my retirement in February 2000 but was not consulted by IRIS on their evaluation of the CIIT BBDR model." "A full examination of the uncertainties associated with empirical modeling of dose-response, side-by- side with the uncertainties that USEPA has identified in the CIIT BBDR modeling, would be informative. For example, one could ask about the relative uncertainty of dosimetry based on CFD modeling in anatomically realistic models of rat and human nasal passages versus empirical modeling of dose- response that does not specifically address dosimetry at all. Ignoring dosimetry does not, and should not, remove concern for the role of dosimetry as a determinant of dose-response. Uncertainty about dosimetry exists for any model of toxicant/carcinogen dose-response. Is a dose-response analysis that explicitly describes dosimetry inherently more uncertain than an approach that wholly ignores dosimetry? This same argument, comparing data-driven and empirical descriptions, can be applied to each of the main components of the BBDR model. Empirical models effectively hide explicit uncertainties about the shapes of the dose-response curve because the empirical models do not acknowledge the mechanistic determinants of dose- the other hand, explicitly describes these determinants. This situation is reminiscent of the early days of PBPK modeling (1980's - 1990's) where PBPK models were sometimes said to increase uncertainty in the characterization of pharmacokinetics relative to empirical PK models. The need here, both for PBPK models and for the BBDR modeling for formaldehyde, is to step back and ask what determines the behavior of interest and to then realize that only relevant data and its inclusion into the dose-response analysis can address these uncertainties. BBDR modeling is simply a tool for integrating data on the mechanistic determinants of dose-response to provide a capability for predicting the entire dose-time response surface." "Issue 3- Labelling index data: ... Notwithstanding the variability in the data, a clear J-shape is apparent [figure B-18 in Appendices], with an initial decrease in labeling with increasing flux to a nadir in the labeling index slightly below a flux of 2,000 pmol/(mm^2- hr). At higher flux values, which are associated with cytolethal effects of inhaled formaldehyde, the labeling index increases, reflecting regenerative cellular proliferation subsequent to cell killing. Heck and Casanova (1999) suggested that DNA-protein crosslinks (DPX) due to inhaled formaldehyde act as physical blocks to the progression of the replication complex along the DNA strand, and			extrapolation of the rat model was demonstrated to be unstable and could not be refined. The revised assessment compares the estimate derived from the CIIT model with the risk at the point of departure derived from the human epidemiology data. EPA Note: regarding issue 7, sensitivity analysis of model predictions is now a required component of assessing model robustness (for example in various PBPK models used by EPA). The constraints used in these analyses are described in the main text and appendix.

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thereby effectively reduced the rate of cell replication…The theory proposed by Heck and Casanova (1999) is supported in more recent literature (e.g. Nakamura and Nakamura 2020)… The J-shaped dose-response for labeling index has significant implications for formaldehyde risk assessment. In the CIIT BBDR model, formaldehyde exerts a low dose linear directly mutagenic effect as a function of the formation of DPX and, simultaneously, the J-shaped dose-response for the rate of cell division. The human version of the CIIT BBDR model (Conolly et al. 2004) predicted a J-shaped dose-response for tumor risk, with risk only increasing above background at about 2 ppm inhaled formaldehyde. This result was, of course, dramatically different from USEPA's assessments, which identify inhalation unit risks in the range of a few ppb. In this context, USEPA makes much of the variability in the labeling index data (see Time variability of labeling data, Appendices, p. B-54). The variability is used to justify alternate dose-responses that do not include the J-shape, including dose- responses that are monotonically increasing in cell division rate as a function of flux/inhaled ppm (e.g. Figures B-24 & B-25, Appendices, p. B-63). These alternative dose-responses can dramatically change the risks predicted by the BBDR model. Given the size and consistency of the Monticello et al. (1991, 1996) dataset, these alternative dose-response exercises are less than convincing… I suggest that USEPA should provide a clearly stated justification for use of cell replication dose-responses that are not J-shaped. If the size and quality of the labeling index data described by Monticello et al. (1991, 1996) is not to be trusted, then what is? … I agree that calculation of division rates as a function of both time (age of rat) and flux is preferable. In fact, this two-dimensional approach is being used in an ongoing update of the BBDR model that is not otherwise considered here. However, USEPA is using this and similar criticisms of the CIIT BBDR modeling of the labeling index data to justify use of alternative, much more empirical dose-response models that do not capture our understanding of the biological processes involved. As noted above, the one-dimensional expression for division rate as a function of flux retains the main qualitative feature of the labeling index dataset, its statistically significant J-shape. Does USEPA really think that an empirical dose-response function that completely ignores the CIIT bioassay labeling index dataset provides greater certainty in the prediction of human risk?” “Labeling index data for bioassay exposure durations from 1 day through 6 weeks (Monticello et al. 1991) were measured by injecting BrdU while subsequent time points (Monticello et al. 1996) used osmotic minipumps implanted for 3 days. Calculation of a division rate constant, which is needed as an input to the clonal growth model, from labeling index data, requires an estimate of the length of the interval over which tissue is exposed to the labeling agent. Since this estimation is problematical for injection studies, the injection data were first transformed			

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to equivalent minipump data using a factor of 6.83, which was the ratio of minipump labeling index to injection labeling index for all the control data. This factor was calculated from a total of 40 data points, 20 from pulse labeling and 20 from pump labeling. Conolly et al. (2003) then used a formula for the conversion of labeling index data into division rate constants due to Moolgavkar and Luebeck (1992). USEPA correctly note that that pulse label data should not be used with this formula. However, they apparently fail to understand that the pulse label data were transformed into equivalent pump data before they were used for calculation of division rate constants (see Maintext p. 2-71 and Appendices, p. B-54, Uncertainty due to combining pulse and continuous labeled data). Thus, the USEPA statements that the use of the Moolgavkar and Luebeck (1992) formula is "extremely uncertain" (Maintext, p. 2-71, line 26) and "problematic" (Appendices, p. B-54, line 17) and is itself problematical." "Issue 6- Use of historical controls: ...When the CIIT BBDR model was developed, we worked with 13 control tumors and did not anticipate the possibility of there being no control tumors. Is it reasonable to use this issue to justify rejection of the CIIT model? USEPA describes numerous alternative versions of the CIIT model in the IRIS Maintext and Appendices and in the supporting publications (Crump et al. 2008; Subramaniam et al. 2007; Subramaniam et al. 2008). Thus, the ability within USEPA to develop alternative versions of the BBDR is not a constraint. Is there a reasonable alternative for scale-up of the CIIT rat BBDR model to the human version that USEPA could have implemented?... The ratio of human to rat basal mutation rates described above and used in Conolly et al. (2004) is a means of accounting for Peto's paradox in the scale-up of the BBDR model from the rat to human. While that approach cannot be used when there are no control tumors, alternative methods of scaling are available. For example: 1) Set up a two-stage clonal growth (MVK) model for the rat nose as in Conolly et al. (2003). 2) Without specifying exposure to formaldehyde or any other chemical, adjust pmutr to produce a small lifetime tumor incidence, say 10-6. Repeat with increasing values of pmutr until lifetime tumor incidence is 100%. This exercise will need to draw on relevant literature for biologically reasonable values of the growth advantage for intermediate cells (cells with one mutation) relative to normal cells (e.g. Conolly and Kimbell 1994). 3) Set up the MVK model for the human respiratory tract as in Conolly et al. (2004). 4) As in 2 above, adjust pmuth to obtain end of life tumor risks from 10-6 to 1.0 (100%).			

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5) The ratio of pmuth to pmutr at given levels of lifetime risk will describe rat to human scaling of the MVK model. The values of pmuth will be several orders of magnitude smaller than the corresponding values of pmutr. 6) This scaling would then be used with the human BBDR model to evaluate cancer risks associated with exposure to formaldehyde. For example, the calculated scaling factor(s) would be used to adjust the value of KMUrat, which defines the relationship between DPX and pmutr, to obtain KMUhuman." ." "Issue 7- Initiated cells: … USEPA (see Maintext, p. 2-73, Kinetics of initiated cells) and Crump et al. (2008) perturb the values of these optimized parameters, particularly the I cell division rate, and show that BBDR model predictions of tumor incidence changes quite dramatically. This is, however, expected behavior when the optimized value of a sensitive parameter is arbitrarily changed…. USEPA appears to not understand that the richness of the datasets for N cells and SCC highly constrains the kinetics of I cells, and specifically the value of the I cell division rate constant. It is just plain wrong to say that there are no relevant data for I cells." *[Please see docket for details and supporting information]*			

Table 3. Other Comments (organized by topic areas)

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IRIS Process	
"The EPA has not allowed for adequate stakeholder engagement during the comment period. Formaldehyde is an environmental justice and affordable housing concern. Lower-income communities are disproportionately at risk of exposure to formaldehyde and resulting health effects from pressed wood products in homes built with less costly building materials. Given this, EPA should have better incorporated into the 60-day comment period opportunities for affected communities as well as academics to engage with EPA on the Formaldehyde Toxicological Review. We have stated our concerns about effectively engaging communities in the public comment process in previous comments submitted to EPA."	UCSF (4)
"We wish to underscore that the formaldehyde draft assessment should be informed by the best available science and developed through a transparent and unbiased process. We are concerned that EPA has neither achieved this objective nor meaningfully conferred with USDA and FDA on pertinent issues related to animal agriculture and food safety."	PEA (1)
"We note several federal agencies have commented on the Draft IRIS Toxicological Review of Formaldehyde (Inhalation), but we did not see comment from FDA or USDA, both of which have familiarity with the animal heath, public health, and food safety uses of formaldehyde."	AVMA (1)
"Moreover, because EPA failed to incorporate fundamental concerns around key issues during the intra-agency and interagency review process, the agency therefore should coordinate with Office of Management and Budget (OMB) to conduct a formal interagency review of the draft formaldehyde IRIS assessment that facilitates review and comment from experts at agencies familiar with use of formaldehyde across the economy (such as FDA and USDA, for example)."	USCC (5)
"At Step 3 of its process, EPA solicits input from other federal agencies. In this case, EPA provided other federal agencies only four weeks to respond to its voluminous materials. While this time would be short under normal circumstances, EPA's 30 days included the period from Christmas through New Year's, a period when many in the federal government are out of the office, further reducing the actual time available for other agencies to review. Perhaps as a result of this, several federal agencies from whom responses should have been expected, did not respond. Given the lack of a clear record on the review, however, we are unable to discern why these agencies did not respond. For this reason, and others discussed below, EPA should reengage with other federal agencies to ensure it has obtained their considered opinions." "EPA has not sought meaningful comment on draft charge questions and peer review committee task, and EPA and NASEM sequencing of public comment, 2022 Draft Assessment revisions, and selection of reviewers undermines the rigor of the peer review." "EPA's draft peer review charge questions[191] unduly narrow the scope of the review, raising key scientific, legal, and policy issues on the quality and independence of the peer review process. For example, there are no questions regarding the 2011 NASEM recommendations on the 2010 Draft Assessment."	ACC (0103; 77, 79, 80, 85, 86) ACC (0092; Attach. #6, 2)

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"With regard to the lack of transparency, EPA has not docketed its responses to the interagency comments on the 2022 Draft Assessment. The failure to document any changes to the 2022 Draft Assessment (including its appendices) based on interagency comment further hamstrings the public's ability to comment on this complex and lengthy document." "The interagency review process conducted on the 2022 Draft Assessment demonstrates why a more structured interagency review process is appropriate, especially for assessments, such as the 2022 Draft Assessment, which have the potential to cause major regulatory and other impacts if they are adopted and used in subsequent regulatory actions. Submitting draft assessments for review under E.O. 12866 as "significant guidance documents" would result in a process that is more transparent, responsive, accountable, deliberate, and advantageous for several reasons." "Consistent with the prior NAS review of this assessment and the valuable NAS feedback to improve the IRIS process as well as EPA's legal and scientific requirements, ACC and the Panel recommend the following steps: 1) Request the Office of Management and Budget to conduct a formal interagency review for the draft formaldehyde IRIS assessment and charge questions prior to their release for public comment. 2) Publish and respond to interagency comments on draft charge questions prior to commencing the public comment period or peer review process. 3) Consistent with EPA[5] and White House policies,[6] take public comment on draft charge questions before initiating the peer review. In light of these clear directives on sequencing, EPA and NAS should evaluate those comments prior to selection of the panel "so that appropriate expertise is included to address all charge questions," and, if appropriate, re-open the nomination process. 4) EPA should incorporate the recommended charge questions (Appendix 1) and those received during the public comment period and update the committee task. 5) EPA should not restrict the committee's task to "responding only to the materials provided by the EPA"." *[Please see docket for details and supporting information]*	
"This comment seeks to highlight for EPA as well as reviewers from the National Academy of Sciences, Engineering, and Medicine the content of relevant feedback in EPA's general IRIS docket (httpw://www.regulations.gov/docket/EPA-HQ-ORD-2014-0211), for which the Agency has directed comments on the IRIS process in recent years (https://iris.epa.gov/Dockets/). Attached are examples of submissions which may be relevant to the review of the draft formaldehyde assessment." *[Please see docket for details and supporting information]*	Anon (0089; 1)
"Also attached are several economic, legal, public policy, and editorial publications highly relevant to this assessment and the IRIS process. [Graham and Liu 2014; Williams 2019; Graham 2006; Logomasini 2020; Logomasini 2019; Dourson 2018]." *[Please see docket for details and supporting information]*	Anon (0090; 1-2)
NASEM Peer Review	
EPA has already taken steps that at a minimum raise questions regarding the appearance of a lack of impartiality. While NASEM has not released a provisional list of panel members who will review the 2022 Draft Assessment, the assessment cites multiple publications coauthored by the Staff Officer with well-documented involvement with the IRIS program, this assessment, the response to the previous	ACC (0103; 83-85)

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NASEM recommendations, and EPA advocacy on this matter. Even if not explicitly prohibited by the above cited NASEM policy, participation of this Staff Officer raises significant issues, particularly as the 2022 Draft Assessment relies on the Staff Officer's publications violates EPA policies on independence and reviewing one's own work. In addition, the solution provided by NASEM's policies for a conflicted or biased panelist who nonetheless is the only source of needed expertise is to "balance" that individual's perspective on the panel, a remedy that is not possible in the case of a conflicted Staff Officer." "The OMB Peer Review Guidance cautions agencies to "avoid repeated use of the same reviewer on multiple assessments unless his or her participation is essential and cannot be obtained elsewhere." EPA Peer Review Handbook uses similar language: "The principle is to avoid the repeated use of the same reviewer on multiple assessments unless his/her participation is essential and the expertise cannot be obtained elsewhere."[180] Despite this clear guidance, the responsible Staff Officer has stated unequivocally that the EPA sponsored NASEM committee will include members from the previous 2011 NASEM committee that reviewed the 2010 draft IRIS formaldehyde assessment."	
"I request that EPA finalize the IRIS Formaldehyde document without the involvement of a committee formed by the National Academies of Science, Engineering and Medicine... The proposed involvement of a NASEM committee in bringing the IRIS document to closure is inappropriate. The NASEM modus operandi with the majority of committees deliberations conducted in closed sessions, out of view of the public, without detailed transcripts is not consistent with EPA's requirements that all EPA Advisory Committee activities be open to the public with the opportunity for public input at each meeting with all proceedings documented and transcripts available to interested parties. The Task Order agreement executed between EPA and the NASEM in the Fall of 2021 should be canceled by mutual agreement of both parties... If you, as EPA Administrator, determine that finalization of the IRIS Document will benefit from input from a Scientific Advisory Committee of qualified experts, you have the legal authority to appoint such a Committee to function with oversight by a qualified EPA Federal Government Employee...In my opinion, the EPA does not need any further advice from the NASEM on this matter. I submit that with each NASEM review there is a potential for Committee members to offer more detailed prescriptive advice for EPA to follow to reach the regulatory conclusions the NASEM Committee members would like from EPA." *[Please see docket for details and supporting information]*	RM (2-3)
Not on the IRIS Formaldehyde Assessment, including on Exposure Assessment and Risk Management Considerations[2]	
"We are concerned about the draft IRIS Risk Assessment as it is not consistent with the scientific and regulatory conclusions on formaldehyde in the European Union." "In the IRIS Risk Assessment, calculated unit risk estimates were in the range of 6.4×10^{-6} and 3.4×10^{-5} per μg/m^3 for the respective cancer types and reference concentrations (RfCs) for non-cancer health effects were derived in the order of 0.001-0.01 mg/m^3. It is worth noting that, as given in the WHO indoor guidance documentation from 2010 and updated in 2017, the formaldehyde concentration in exhaled air from humans is just in the same range: "Human exhaled air contains formaldehyde in concentration in the order of 0.001–0.01 mg/m^3, with an average value of about 0.005 mg/m^3". Formacare would recommend putting the unit risk estimates	Form (0085a; 1-2)

[2] IRIS assessments are not risk assessments and they do not address exposure assessment or risk management considerations. These are the purview of other EPA program and regional offices.

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and RfCs for the respective diseases in perspective with the respective prevalence considering actual exposures. This could avoid that the assessment misses capturing the possible risk from formaldehyde exposure in indoor environments and at the workplace."	
"Additionally, the exposure limits and dose response criteria (i.e., Reference Concentrations and Inhalation Unit Risk Factors) proposed are 100 to 1000 times more stringent than the exposure limits/dose response criteria recently established or under consideration in the European Union. These 'protective' concentration limits are similar to concentrations in human breath and are at or below the background formaldehyde concentrations in rural air."	USCC (5)
"While ILMA members understand EPA's interest in protecting consumers and workers, their experience is that the use of formaldehyde-release biocides have resulted in few issues over decades of use. In part, this is due to an evolving industrial landscape, including increased ventilation, PPE, and safety protocols to reduce well-known and studied hazards, like those caused by the proliferation of microbiological toxins. MWF companies are concerned that, by EPA's ill-supported Draft Assessment, one of the most powerful tools for worker protection will be effectively compromised."	ILMA (2)
"From our initial review of EPA's formaldehyde assessment, we note that there is no descriptive reference or acknowledgement of the presence, use, benefit or possible hazards associated with formaldehyde applications in the animal agriculture sector."	PEA (1)
"On p. 3-29 'An overall RfC for formaldehyde of 0.007 mg/m^3 was selected. This value is within the narrow range (0.006-0.009 mg/m^3) of the group of respiratory system-related RfCs, which together are interpreted with High confidence (sensory irritation, pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control.' EPA guidelines allow a considerable degree of freedom in identifying LOAELs, NOAELs, modeling dose-response, and selecting uncertainty factors. The statement above, however, gives the appearance of conclusions being targeted to a pre-determined number." "Inappropriately the Draft Assessment does not justify the large quantitative differences in EPA's hazard and dose-response assessments when compared to recently published exposure guidelines and limits by both WHO and the European Commission, respectively. Each of these authoritative bodies derived safe exposure levels up to three orders of magnitude higher than the safe exposure limits (RfCs and IURs) presented in the Draft Assessment." "As such, the Draft IRIS Assessment should be benchmarked against competent authority evaluations [WHO, SCOEL, ECHA] performed under similar assessment guidelines. Additionally, any substantial deviations from other competent authorities conclusions must be documented and discussed in the Draft IRIS Assessment. Any further revisions to the Draft Assessment, must address the major differences between the derived no-effect levels (DNELs) and Occupational exposure limits (OELs) when compared to the RfCs and IURs proposed." "The Draft Assessment reaffirms the oral RfD developed in 1990 and is currently on IRIS. This exposure limit raises public concern unduly with little likelihood of any recognizable health benefits...A simple ground truthing demonstrates the inappropriate degree of conservatism in the medium confidence RfD. It is well known that formaldehyde is an endogenously produced natural product of metabolism. In addition, there are many studies of the naturally occurring concentrations of formaldehyde in food. For example, in their evaluation of the literature regarding background concentrations of formaldehyde in food, the European Food Safety Authority (EFSA, 2014) calculated the mean concentration of formaldehyde in foods to be 100 mg/kg. Assuming an average human body weight of 70 kg and the oral RfD of 0.2 mg/kg/day, the safe oral dose is 14 mg/person/day. Assuming consumption of 1 kg of food/day/70 kg human, the	ACC (0092; Attach. #4, 2) ACC (0092; Attach. #5, 2, 3-4) ACC (0100; 45, 46, 60, 67-68)

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average human ingests 100 mg formaldehyde/day. As such, our normal diet exceeds the safe exposure level by 7 times the allowable limit. Clearly, this does not reflect actual risk, is not derived from the best available science, is overly conservative, and unnecessarily alarmist." "In addition, EPA has signaled that, in the formaldehyde risk evaluation under the amended Toxic Substances Control Act (TSCA), it "plans to include information developed from the draft IRIS hazard and dose response assessment."8 The push to use draft IRIS information in a regulatory setting without finalizing the assessment or addressing comments on the underlying work product runs contrary to EPA policies and ACC comments on the scoping document. It also suggests that the Agency' rush to deploy the draft could short-circuit a rigorous peer review process." "U.S. EPA's use of draft assessment violates statutory requirements for "Best Available Science"...Perhaps most concerning, U.S. EPA has signaled that, in its forthcoming draft and final formaldehyde risk evaluation under TSCA, it "plans to include information in a regulatory setting prior to finalizing the assessment, by incorporating both public and peer review comments, runs contrary to EPA policies and would render superfluous both public comment and a rigorous peer review process." "EPA's failure to proactively discourage use of draft assessment violates agency policies. Failure to proactively prevent use of the draft IRIS assessment by those inside and outside the Agency would contradict long-standing EPA policies on peer review, information quality, and intergovernmental collaboration." *[Please see docket for details and supporting information]*	